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REVIEW ARTICLE

Effects of photobiomodulation in the treatment of fractures: a systematic review and meta-analysis of randomized clinical trials

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Abstract

Several therapeutic strategies have been proposed to optimize the conventional treatment of fractures. Photobiomodulation (PBM) appears to help reduce pain and control inflammation, and it also accelerates bone repair. This systematic review aimed to evaluate the effectiveness and safety of PBM with low-level laser therapy (LLLT) in the bone fracture healing process. We included randomized controlled trials (RCTs) comparing the effects of PBM with those of any other intervention in adults with lower or upper limb bone fractures. The primary outcomes investigated were pain reduction, radiographic healing, and adverse events. The searches were conducted in October 2018. Two RCTs were included that compared PBM to the placebo. A meta-analysis showed significant difference in favor of PBM for pain reduction (MD 1.19, 95% CI [0.61 to 1.77], 106 participants, two RCTs), but this difference was not clinically significant. One RCT (50 participants) showed a clinical and statistical improvement in physical function (MD − 14.60, 95% CI [− 21.39 to − 7.81]) and no difference in radiographic healing, regarding absence of fracture line (RR 1.00, 95% CI [0.93 to 1.08]) and visible bone callus (RR 0.33, 95% CI [0.01 to 7.81]). The certainty of evidence was classified as low to very low. Based on the evidence of low to very low certainty, PBM seems to be associated with the improvement of pain and function. Therefore, new RCTs are required that meet the recommendations of CONSORT to prove the effectiveness and safety of this intervention and support its recommendation in clinical practice.

Keywords Low-level light therapy · Fracture healing · Meta-analysis

Introduction

Bone fractures are considered the most common traumatic injuries in humans [1]. Under ideal conditions, complete repair is achieved in 6 to 8 weeks [2]. However, systemic factors (diabetes, osteoporosis, and nutritional deficiency, among others), habits (smoking, alcohol consumption), the involvement of adjacent tissues, and the characteristics of the injury itself (infection, gap between fragments, and/or displacement of fragments) may increase the repair time or even prevent regeneration [1–3].

Several therapeutic strategies have been proposed to optimize the conventional treatment outcomes of fractures, particularly in the most complicated cases [1–4]. Recent proposals include cell therapy using stem cells combined or not with growth factors and/or bioactive molecules, biomaterials that serve as scaffolds, mechanical stimuli, and photobiomodulation (PBM) [1–8].

PBM consists of using a light source for therapeutic purposes, and red and near-infrared light sources are the most

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commonly used. The PBM application can reduce pain, control the inflammatory reaction, and accelerate repair in several types of injury. Its action mechanism is based on the absorption of light by cellular chromophores (in particular the cytochrome C oxidase enzyme of the mitochondrial respiratory chain), generating an increase in energy production (ATP), in addition to an increase in the production of nitric oxide, the modulation of calcium levels, and the activation of several transcription and protein synthesis factors responsible for the observed therapeutic effects that are directly correlated with the correct choice of dosimetric parameters [9].

Some studies, including systematic reviews, have reported the effects of PBM on bone repair. More specifically, these studies have evaluated bone lesions in animal models [4, 10], different applications in the bone repair processes of the human maxillofacial complex [11–15], and the bone cells themselves in in vitro models [16]; however, no reviews on the effects of PBM for bone fracture treatment were found. Therefore, the aim of this systematic review was to evaluate the effectiveness and safety of PBM with low-level laser therapy (LLLT) for bone fracture healing.

Materials and methods

This systematic review that was conducted followed the methodology described in the Cochrane Handbook for Systematic Reviews of Interventions [17], and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18]. The protocol is registered on the PROSPERO database of systematic reviews (available at https://www.crd.york.ac.uk/prospero/) under the number CRD42018093594.

Criteria for considering studies for this review

We included randomized controlled trials (RCTs) with a parallel design that evaluated the use of PBM with LLLT in adult individuals (aged 18 years and older) with lower and/or upper limb fractures. The RCTs considered were those that evaluated any type of PBM with LLLT (with different parameters such as wavelength, dose, and duration) compared to placebo (sham), no intervention, or other nonsurgical interventions (e.g., therapeutic ultrasound, shock wave therapy, among others). We also included studies that evaluated the use of PBM with LLLT as an isolated procedure or combined with other conservative interventions, provided that the same interventions were used in the individuals in the control group. Studies with multiple interventions where the effects of LLLT could not be evaluated alone were excluded.

The following outcomes were measured:

1. Primary outcomes: pain reduction, assessed by any validated scale, such as a visual analog scale (VAS) [19]; radiographic healing, evaluated by simple radiography; and any adverse event resulting from the intervention
2. Secondary outcomes: physical function and quality of life, assessed using validated scales, such as the 36-Item Short-Form Health Survey (SF-36) [20]; and patient satisfaction with treatment outcomes

All assessment time points reported by the authors of the included RCTs were considered.

Search methods for identifying studies

The search was performed on October 10, 2018, in the electronic databases: MEDLINE (Medical Literature Analysis and Retrieval System Online) via PubMed, Embase (Excerpta Medica Database) via Wiley, CENTRAL (Cochrane Central Register of Controlled Trials) via Wiley Cochrane Library, LILACS (Literatura Latino-Americana e do Caribe em Ciências da Saúde [Latin American & Caribbean Health Sciences Literature]) via Biblioteca Virtual em Saúde [Virtual Healthcare Library] (BVS), PEDro (Physiotherapy Evidence Database), CINAHL (The Cumulative Index to Nursing and Allied Health Literature) via EBSCOhost, Scopus via EBSCOhost, and SPORTDiscus via EBSCOhost.

The registry records of ongoing or recently completed RCTs were also used: ClinicalTrials.gov (available at: www.clinicaltrials.gov), ICTRP (International Clinical Trials Registry Platform), and WHO (World Health Organization) (available at: http://apps.who.int/trialsearch/default.aspx). A search of the gray literature was performed in the Open Gray database (available at: http://www.opengray.eu/). Manual searches were also performed in the reference lists of relevant articles. There were no restrictions regarding the language, the year of publication, or the publication status (published studies, unpublished, published as reports or abstracts, or studies in progress). The search strategies are presented in Online Resource 1.

Selection of studies and data extraction

Two reviewers (FCJN and ALCM) independently assessed the titles and abstracts of the studies obtained through search strategies using the Rayyan platform (https://rayyan.qcri.org). The studies with potential for inclusion were analyzed by reading the full text of the article. A third author (KPSF) was consulted in cases of disagreement between reviewers. Two reviewers (FCJN and ALCM) independently extracted the data from each RCT included using a standardized form that included information on eligibility criteria, methodological aspects, the characteristics of the participants and the

intervention, comparator groups, the outcomes analyzed, the follow-up time, and the relevant results.

Assessment of risk of bias in included studies

Two reviewers (FCJN and ALCM) independently assessed the risk of bias in each study included in the systematic review using the risk of bias assessment tool proposed by the Cochrane Collaboration [21]. This tool is composed of seven evaluation domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. The risk of bias assessment for each of the domains involves classification into three categories: (1) low risk of bias, when the domain described by the study is considered adequate; (2) high risk of bias, when the domain described by the study is considered inadequate; and (3) unclear risk of bias, when the study presents insufficient information for assessing the risk of bias.

Data synthesis and measures of treatment effect

When possible (homogeneous studies and available data), the results of the studies were pooled in a meta-analysis (quantitative synthesis) that was presented in the form of forest plots generated by Review Manager Software version 5.3 [22]. For the dichotomous outcome data, the relative risk (RR) was calculated with a 95% confidence interval (95% CI). For the continuous outcome data, the mean difference (MD) (95% CI) was calculated. The random effects model was used in all meta-analyses [17].

Assessment of heterogeneity

The presence of heterogeneity, considered as any variation among the studies included in the review, was evaluated according to clinical, methodological, and/or statistical heterogeneity. The presence of statistical heterogeneity between the studies was detected by the chi-square test (χ^2). The degree of heterogeneity was assessed by the I^2 statistic, with I^2 values above 50% considered to represent significant heterogeneity between studies within the same meta-analysis [17].

Subgroup and sensitivity analysis

We planned to perform the following subgroup analyses: type of fracture (acute trauma versus repetitive trauma) and conservative versus surgical treatment. We also planned to conduct a sensitivity analyses to evaluate the robustness of the results and the various methodological aspects, excluding those from the analysis studies with high risk, those with missing data, and those reported only in abstract form. However, because of the missing data, it was not possible to perform these planned analyses.

Publication bias assessment

We planned to evaluate the publication bias using funnel plots if 10 or more RCTs were included in the same meta-analysis. However, this evaluation was also not possible due to missing data since only two studies were included in the review.

Assessing the certainty of the evidence

Two review authors (FCJN and ALCM) independently assessed the certainty of the evidence for primary outcomes (pain and radiographic healing) according to the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation Working Group) [23], which classifies the evidence based on five domains: methodological limitations (risk of bias), inconsistency, indirectness, imprecision, and publication bias. The certainty of a body of evidence was assessed using the GRADEpro GDT software and was classified as high, moderate, low, or very low. The reasons for downgrading the certainty of evidence were presented in details in the summary of findings table.

Results

The database search resulted in a total of 878 references. After removing 309 duplicate references, 569 were analyzed by reading the title and abstract, and three were considered potentially eligible and read in full-text. One study was excluded because it did not include the appropriate population (individuals suspected of having a stress fracture) [24]. Thus, two RCTs [8, 25] were included in this systematic review (Fig. 1). Moreover, two ongoing studies were identified with only protocols available (NCT02749929; NCT03014024) (Online Resource 2).`

Characteristics of the included studies

Table 1 details the characteristics of each included study. We included two parallel RCTs [8, 25] published in 2014 in English that were conducted in Iran and China. The studies involved a total of 104 participants, with samples ranging from 50 to 54 participants. The mean age ranged from 24.6 to 32.6 years. One study [8] reported that 58% of the participants were men, but the other study did not provide information on the participants' sex.

The study by Nesioonpour et al. [25] included individuals diagnosed with a tibial fracture who were surgically treated with an interlocking intramedullary nail. The study by Chang et al. [8] included individuals with a closed fracture of the phalangeal bone, metacarpal bone, carpal bone, distal ulna,

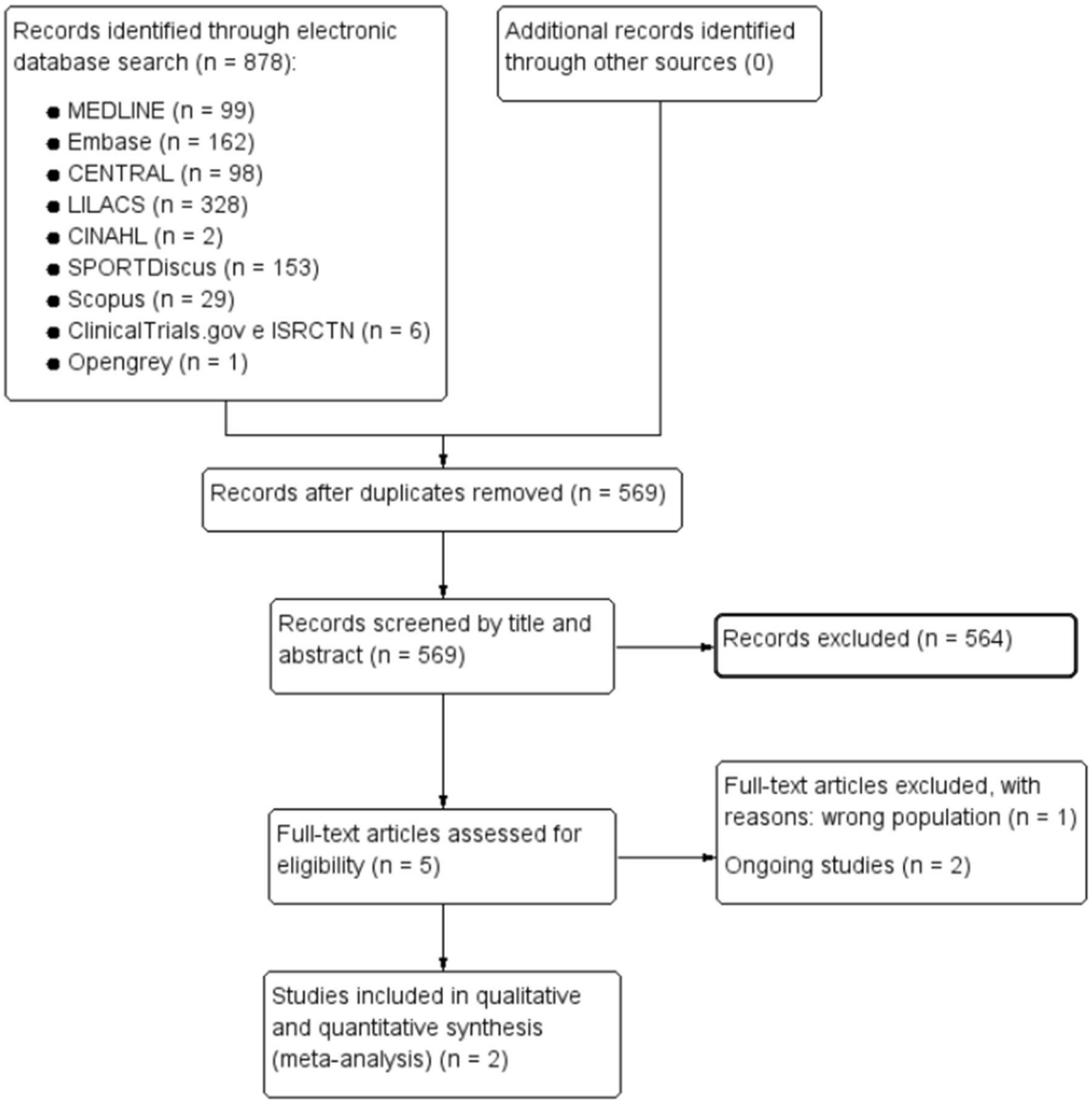


Fig. 1 PRISMA flow diagram of the study selection process

or distal radius; all fractures were treated conservatively. Nesioonpour et al. [25] excluded pregnant women; individuals with malignant or benign tumors with malignant potential; and individuals with hypersensitivity to light, e.g., in cases of systemic lupus erythematosus, coagulopathies, high intracranial pressure, history of chronic pain, and prolonged use of opioids or other analgesics during the month prior to the study. Chang et al. [8] did not describe the exclusion criteria.

The participants in both studies were divided into two treatment groups: (1) the intervention group, which received PBM with LLLT; and (2) the control group or placebo, which received sham laser treatment (off mode) emitted at the fracture site. The devices were identical, and the treatments had the same time duration and laser application points.

The two studies evaluated the intensity of pain at the fracture site using the VAS, and only one study assessed the radiographic healing of the fracture and the individual's physical function. Adverse events, quality of life, and patient satisfaction were not assessed by either of the studies included in this review.

Results of the risk of bias assessment

Both studies did not provide sufficient information about the randomization process and the allocation concealment and were thus classified as having an unclear risk of selection bias. The two studies adequately described the blinding of participants and outcome assessors (placebo-controlled double-blind) and were classified as low risk of bias for these domains (performance bias). In both studies, all randomized participants completed the study; thus, the studies were considered as low risk of bias for the incomplete outcome data domain

Table 1 Characteristics of the included studies

Study	Chang et al. (2014)[8]	Nesioonpour et al. (2014) [25]
Methods	Parallel RCT Collection period: 2009 to 2011 Study location: Taiwan, China	Parallel RCT Collection period: 2012 to 2013 Study location: Ahvaz, Iran
Participants	$N = 50$ (58% women) Hand and wrist fractures treated conservatively	$N = 54$ (sex not reported) Tibial fracture treated surgically with IMN
Intervention	PBM ($N = 25$) Pulsed diode laser: · Wavelength 830 nm · Average power 60 mW · Dose 9.7 J/cm^2 · Area 3.7 cm^2 · Time 600 s per each fracture site	PBM ($N = 28$) Combination of two lasers: 1- Continuous GaAlAs diode laser (IR): · Wavelength 808 nm · Average power 300 mW · Dose 6 J/cm^2 · Area 1 cm^2 · Time 20 s per point 2- Continuous GaAlInP diode laser (R): · Wavelength 650 nm · Average power 100 mW · Dose 3 J/cm^2 · Area 1 cm^2 · Time 30 s per point
Treatment time	Treatment time per each fracture site: 10 min (600 s), once a day, 5 days a week, for 2 weeks.	Time 50 s per point (9 J/cm^2) (medial, lateral, anterior, and posterior sides of the fracture region). Only on the first postoperative day. Muscles and surgical wounds were radiated (6 to 8 points) with 4 J/cm^2 (10 s of each: 808 nm at 3 J/point and 650 nm at 1 J/point).
Control	PBM Placebo ($N = 25$) Laser in turn-off mode, same duration	PBM Placebo ($N = 28$) Laser in turn-off mode, same duration
Outcomes	Pain (VAS) Radiographic signs of bone healing: - absence of fracture line - cortical bridging (callus formation) Function (DASH questionnaire)	Pain (VAS)
Evaluations (follow-up)	Before, immediately after the PBM application, and after 2 weeks of treatment	2, 4, 8, 12, and 24 h after surgery

RCT Randomized clinical trial, *N* number of participants, *PBM* photobiomodulation, *nm* nanometers, *mW* milliwatt, *J/cm^2* Joules per square centimeter, *cm^2* square centimeter, *IMN* intramedullary nail, *GaAlAs* galium-aluminum-arsenide laser, *GaAlInP* phosphide indium-gallium-aluminum, *IR* infrared, *R* red, *VAS* visual analog scale, *DASH* Disabilities of the Arm, Shoulder, and Hand questionnaire

(attrition bias). The two studies did not provide a registration of the study protocol and were classified as unclear risk bias for the selective reporting domain (reporting bias). Both studies had an unclear risk of bias for the domain of other sources of bias because all types of fractures regardless of severity were evaluated together, and it was not possible to estimate to what extent this may influence the results given that the evaluated outcomes were pain and radiographic healing of the fracture (Fig. 2).

Effects of intervention

Pain reduction

Despite the variations between the studies, it was possible to pool their data in a meta-analysis (106 participants) to evaluate the isolated PBM effect for local pain, regardless of the type and severity of the fracture, the treatment performed (conservative or surgical), and the duration of PBM therapy. There was a statistically significant difference in favor of PBM for pain reduction, measured by VAS (0 to 10, lower score better), at the end of the treatment (between 1 day and 2 weeks) (MD 1.19, 95% CI 0.61 to 1.77, 106 participants, two RCTs). There was no statistically significant heterogeneity between the studies ($I^2 = 0\%$) (Fig. 3).

Radiographic healing

Only the study by Chang et al. [8] (50 participants) assessed fracture healing using radiographic image (anteroposterior and lateral views) and analyzed the fracture line and bone callus formation after 2 weeks of treatment. No statistically significant differences were observed between groups for both analyses (Fig. 4):

1. Absence of fracture line (RR 1.00, 95% CI 0.93 to 1.08)
2. Visible bone callus (RR 0.33, 95% CI 0.01 to 7.81)

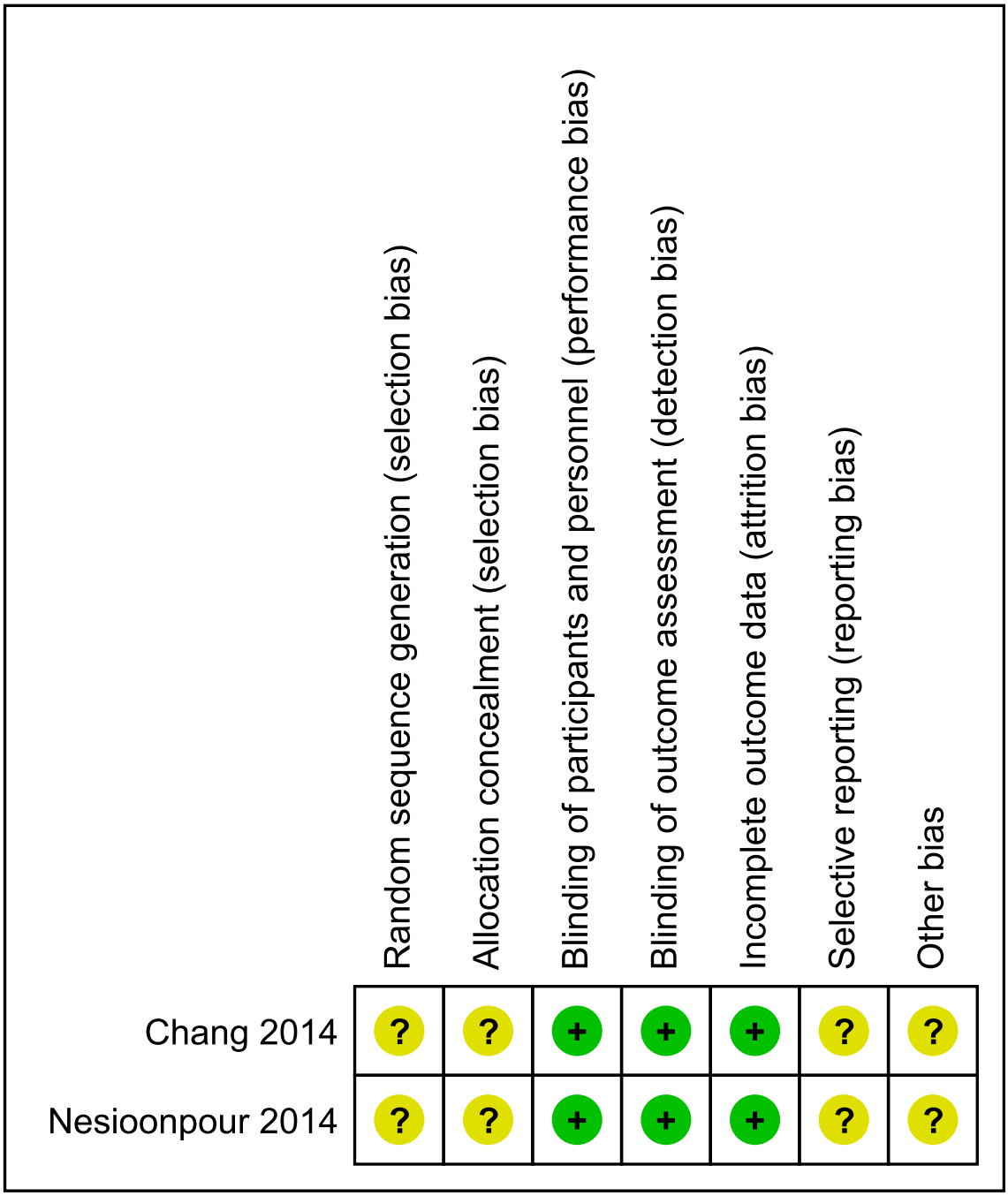


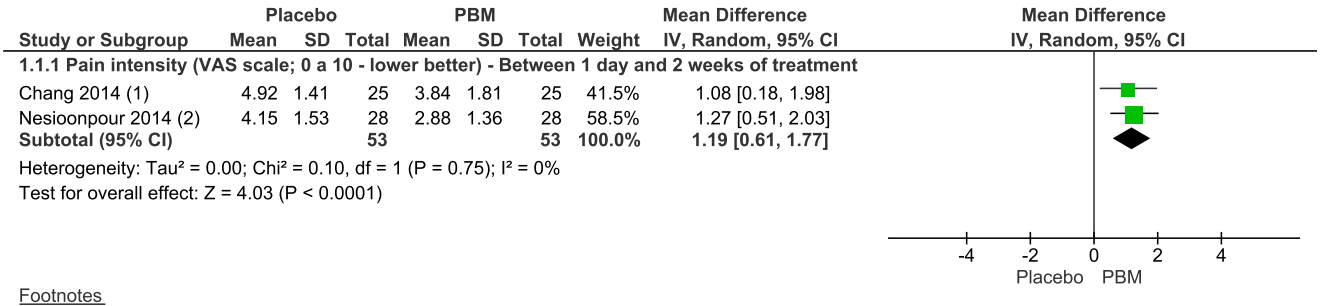
Fig 2 Risk of bias summary of the included studies for each domain. (+) = low risk of bias; (?) = unclear risk of bias

Physical function

Only the study by Chang et al. [8] (50 participants) evaluated the physical function of the participants using the DASH questionnaire (0 to 100, lower score better). There was a statistically significant difference in favor of the group who underwent PBM treatment after 2 weeks of treatment (MD − 14.60, 95% CI − 21.39 to − 7.81) (Fig. 5).

Certainty of the evidence

The certainty of evidence for the main comparison (PBM versus placebo) was classified as "very low" for pain reduction, which indicates that we are uncertain whether LLLT reduces pain compared to placebo, and "low" for radiographic healing, which represents that LLLT may make little or no difference to radiographic healing compared to placebo.



Footnotes
(1) Therapy scheme: once a day, 5 days/week, lasting 2 weeks.
(2) Therapy scheme: 24 hours after surgery.

Fig 3 Forest plot of the meta-analysis for photobiomodulation (PBM) versus placebo regarding pain reduction

There was a downgrade in the levels of evidence due to the methodological quality of the studies, the therapeutic scheme that does not correspond to the clinical practice (only one PBM application), the different types of fractures analyzed together, and the small sample size. Table 2 shows the summary of findings of GRADE assessment.

Discussion

This systematic review conducted a wide literature search to evaluate the effectiveness and safety of PBM with LLLT in individuals with bone fractures. We included two RCTs that compared PBM with placebo [8, 25]. Despite the differences between the types of fractures and the type of intervention, the meta-analysis of these studies showed that the use of PBM seems to be associated with decreased pain, although the evidence has been classified as very low certainty, indicating that new studies may change the estimate of this effect. Therefore, these results should be interpreted with caution. Furthermore, there was no minimal clinical importance difference (MCID) between PBM and placebo for pain (MD = 1.9 points). According to Lee et al., the minimum difference for the VAS for acute pain is three points [26].

Only one RCT [8] evaluated the radiographic changes after the use of PBM in individuals with surgically treated tibial fractures, and no differences were observed between the groups regarding the absence of the fracture line or callus formation. However, this evidence was considered of low certainty, indicating that the confidence in this effect estimate is limited. None of the studies evaluated the adverse events resulting from the intervention; consequently, it was not possible to analyze the safety of the PBM for the treatment of fractures. Finally, the results of only one RCT [8] showed a clinically and statistically significant difference for the physical function of individuals with hand fractures in favor of PBM (DASH score, MCID = 10.83 points [27]).

We did not find any similar systematic reviews to compare our results against. Two systematic reviews indicated that PBM positively affects bone remodeling after surgical and/or orthodontic expansion of the maxillary bone [13, 14]. In addition to the positive results for bone repair, two other systematic reviews that included different postoperative situations of mandibular and maxillary bone repair (extractions, distraction osteogenesis, orthodontic movement, periodontal disease, and cysts) also displayed improvements in pain, inflammation, and healing [11, 15]. In a systematic review, Weber et al. [12] evaluated the effects of PBM with LLLT in the repair of mandibular osteonecrosis due to bisphosphonate use and concluded that PBM showed positive effects, particularly when combined with antibiotic use and minimally invasive surgery with high-level lasers.

In all the aforementioned studies and in the present systematic review, the lack of standardization of the dosimetric parameters, the number of applications, and the evaluation periods was evident. The correct choice of dosimetric parameters (mainly wavelength, power, irradiance, radiant exposure and energy) is fundamental for the success of this therapy. Thus,

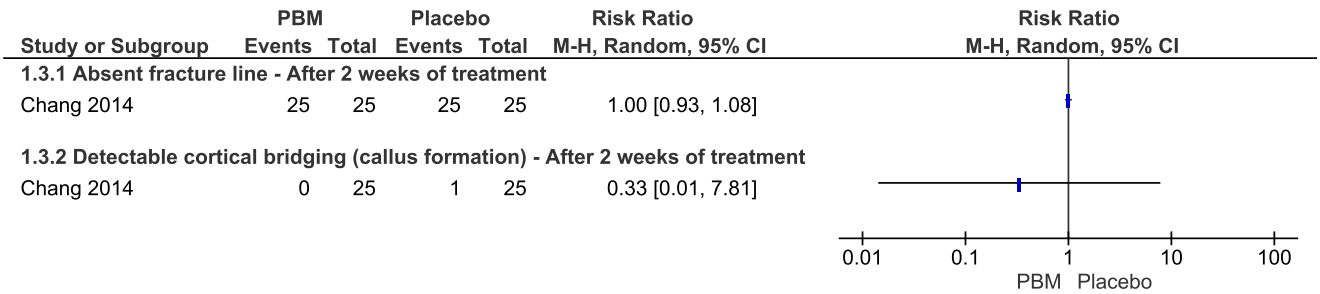


Fig 4 Forest plot for photobiomodulation (PBM) versus placebo regarding radiographic healing

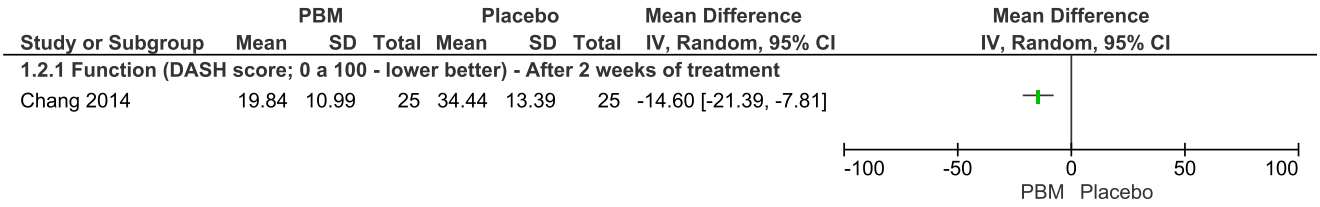


Fig 5 Forest plot for photobiomodulation (PBM) versus placebo regarding physical function

Table 2 Summary of findings table (GRADE assessment)

Photobiomodulation compared to Placebo for Fractures

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with Placebo	**Risk with LLIT**			
Pain intensity (VAS scale; 0 to 10) Follow-up range: 1 day to 2 weeks	The mean pain intensity was **4.15** points	The mean pain intensity in the intervention group was 1.19 points higher (range, 0.61 to 1.77 higher)	-	106 (2 RCTs)	⨁◯◯◯ VERY LOW [a,b,c]
Radiographic signs of bone healing (Absent fracture line) Follow-up: after 2 weeks of treatment	1.000 per 1.000	**1000 per 1.000** (930 to 1.000)	**RR 1.00** (0.93 to 1.08)	50 (1 RCT)	⨁⨁◯◯ LOW [a,c]
Radiographic signs of bone healing (Callus formation) Follow-up: after 2 weeks of treatment	40 per 1.000	**13 per 1.000** (0 to 312)	**RR 0.33** (0.01 to 7.81)	50 (1 RCT)	⨁⨁◯◯ LOW [a,c]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

[a] Downgraded one level due to methodological limitations (insufficient information on randomization and allocation concealment).

[b] Downgraded one level due to different types of fractures and different treatment schemes—only one FBM application session—which does not correspond to clinical practice, in addition to the different types of fractures analyzed together.

[c] Downgraded one level due to the small sample size

once the optimal dose is reached, the response may decrease, stop, or even be contrary to the desired response with the use of higher doses [9].

The strengths of the present study were the extensive search in several databases in the literature, making it unlikely that any relevant studies were missed, and the methodological rigor because it followed the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [17] and PRISMA guidelines [18].

The limitations of this study are related to the lack of RCTs on the PBM application after bone fractures and the low evidence level of the findings, increasing the uncertainties about the estimate and magnitude of the effect.

Thus, as implications for clinical practice, despite the poor quality of evidence found thus far, PBM appears to have some benefit for pain reduction and physical function compared to placebo. However, future RCTs with good methodological quality are essential to prove the effectiveness and safety of this intervention. Future RCTs should follow the recommendations of CONSORT (Consolidated Standards of Reporting Trials) [28], in addition to seeking to define the best combination of dosimetric parameters of PBM, and should evaluate the occurrence of possible adverse events resulting from the intervention.

Conclusion

This systematic review included two RCTs that compared photobiomodulation (PBM) with low-level laser therapy (LLLT) to placebo for the treatment of bone fractures in adult individuals. Based on evidence of low to very low quality according to GRADE, PBM appears associated with improvements in pain and physical function. Therefore, new RCTs are required that follow the CONSORT recommendations to prove the effectiveness and safety of this intervention and support its recommendation in clinical practice.

Compliance with ethical standards

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

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent is not applicable in this study.

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