

## Study Protocol and pre-protocol

Efficacy and safety of photobiomodulation on non-infected pressure ulcer in adults: systematic review protocol of randomized clinical trials

### 1.ABSTRACT

Pressure injuries (PIs) are a significant public health issue, causing harm and compromising the safety of hospitalized patients. Some studies suggest that photobiomodulation may promote anti-inflammatory effects and wound revascularization, accelerating the healing process in skin wounds. However, the quality of evidence remains limited. Objective: To evaluate the effectiveness and safety of photobiomodulation as a treatment for non-infected PIs in adults. Methods: It followed the methodological guidelines of the Cochrane Handbook for Systematic Reviews of Interventions and the PRISMA Statement. A systematic search for randomized controlled trials (RCTs) will be conducted in databases from their inception to December 2024 without language restrictions. The databases included MEDLINE, EMBASE, CENTRAL, LILACS, BBO, ICTRP, ClinicalTrials.gov, WHO, and OpenGrey.

**PROSPERO Registration Number:** CRD42020200637

**Keywords:** systematic review, pressure injury, photobiomodulation, wound healing

### 2.Introduction

Pressure injuries are lesions of the skin and soft tissues resulting from constant or prolonged pressure on the skin (Zaidi, 2023). They are sometimes debilitating, significantly impacting quality of life. These ulcers typically occur in bony areas of the body, such as the ischium, greater trochanter, sacrum, heel, malleolus (lateral and medial), and occipital region. They primarily affect individuals with limited mobility with difficulty changing posture (Zaidi, 2023). According to a recent meta-analysis, the global prevalence of pressure injuries is 12.8% (Li, 2020). In hospital settings, the estimated prevalence is 8.4% (Li, 2020), while in acute care environments, the prevalence ranges from 6% to 18.5% (Tubaishat, 2018). Treating hospital-acquired pressure injuries represents a significant financial burden for healthcare systems. The annual cost of treating pressure injuries in the United States ranges from \$3.3 billion (Van Den Bos, 2011) to \$11 billion (Brem, 2010).

Pressure injuries are classified into four stages according to the National Pressure Ulcer Advisory Panel (NPIAP, 2016), based on the degree of tissue damage (Edsberg et al., 2016). Stage I involves redness in a bony prominence area without visible blanching. In Stage II, skin ulceration occurs, potentially with exudate-filled blisters. Stage III is characterized by the loss of epidermis with possible exposure of subcutaneous adipose tissue and localized necrosis. In Stage IV, there is exposure of muscle, tendon, or bone (NPIAP, 2016). Nurses use assessment scales to determine the risk of developing pressure injuries and assess the vulnerability of hospitalized individuals (Salgado et al., 2018). There are approximately 40 scales for evaluating the risk of pressure injuries, developed based on expert opinions or adapted from other tools.

Treatment begins with a systematic evaluation of the pressure injury, including identifying its location, category, area, characteristics, type of tissue, condition of adjacent skin, and pain monitoring (Edsberg et al., 2016; NPIAP, 2019). Recommendations include cleaning the wound, removing devitalized tissues, treating infections and biofilms, and applying dressings according to the characteristics of the injury (Reddy, 2015). In severe cases, surgical treatments such as amputation, sutures, debridement, or physical approaches like hyperbaric chambers, negative pressure therapy, electrical stimulation, or electromagnetic therapies may be indicated (Gushiken et al., 2021a).

Photobiomodulation (PBM) is a treatment that uses non-ionizing low-intensity light to stimulate tissues. PBM is a non-thermal process that stimulates endogenous chromophores (Andrade, Clark, Ferreira, 2014b). The light used for this therapy typically has wavelengths of 600 to 700 nanometers (nm) and 780 to 1100 nm (Freitas, Lucas, Hamblin, 2017a). Some authors (Jana Neto et al., 2023) have demonstrated that PBM is a safe and effective treatment for reducing healing time in soft tissue wounds associated with bone fractures. A recent systematic review described PBM as effective in promoting the healing of pressure injuries in adult and elderly patients; however, it did not significantly reduce healing time (Petz et al., 2020). This study aims to evaluate whether photobiomodulation is an effective and safe treatment for non-infected pressure injuries in adults.

### **3. METHODS**

#### **3.1 Study Design**

This systematic review was conducted following the methodological recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins et al., 2011) and the reporting recommendations of the PRISMA statement (Moher et al., 2009). The protocol was prospectively registered in PROSPERO (International Prospective Register of Systematic Reviews) under CRD42020175634.

#### **3.2 Eligibility Criteria for Including Studies**

The research question for this study was developed following methodological guidelines for systematic reviews. It utilized the PICO framework—Patient,

Intervention, Comparison, and Outcomes—to formulate the question and select studies. See Table 1.

Table 1 – PICO Framework

Population	Individuals with pressure injuries
Intervention	Use of photobiomodulation/low-level laser therapy
Comparison	Conventional dressings or any other treatment
Outcomes	Tissue repair
Time	Healing time (days, weeks, months, and years)

### **3.3 Review Question**

Is photobiomodulation an effective and safe treatment for non-infected pressure ulcers in adults?

### **3.4 Types of Studies to Be Included**

Randomized clinical trials (RCTs) with a parallel design will be considered.

### **3.5 Population**

Adults (18 years and older) with non-infected pressure ulcers.

### **3.6 Intervention**

Photobiomodulation using LED or laser at any wavelength.

### **3.7 Comparator**

Placebo, no intervention, or other control interventions compared to photobiomodulation.

### **3.8 Outcomes of Interest**

The primary outcomes of interest are pain relief (measured by validated scales such as the Visual Analog Scale), health-related quality of life (HrQoL, measured by validated questionnaires), major adverse events, hospitalization, mortality, wound size reduction (measured with instruments like direct ruler measurements or photography), and pressure ulcer resolution over time (measured in days, months, or years).

Secondary outcomes include any adverse events, the proportion of participants experiencing at least one adverse event during or after treatment (e.g., allergic reactions), reduction in pro-inflammatory cytokines, and an increase in anti-inflammatory cytokines (measured using ELISA assays). Patient acceptability of the intervention will also be evaluated.

### **3.9 Search Strategies for Study Identification**

A comprehensive literature search will be conducted without restrictions on language, date, or publication status. Search strategies will be developed for the following databases: MEDLINE (via PubMed), The Cochrane Central Register of Controlled Trials

(CENTRAL) (via Wiley), Literatura Latino Americana em Ciências da Saúde e do Caribe (LILACS, via Biblioteca Virtual em Saúde - BVS), and EMBASE (via Elsevier).

We will also search ongoing clinical trials through WHO's International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov. Grey literature will be identified via DANS Easy. A hand search will include contacting field specialists, reviewing reference lists of relevant studies in the systematic review, and screening abstracts from specific conference proceedings.

### **3.10 Selection of Studies and Data Extraction**

Using the Rayyan software, two authors will independently screen abstracts and titles retrieved through the search strategy. Based on inclusion criteria, references will be coded as "potentially eligible" or "excluded." To confirm eligibility, full-text articles of "potentially eligible" references will be reviewed. Two authors will also independently perform data extraction using a pre-established data extraction form (in an Excel datasheet). Any disagreements during selection or extraction will be resolved by consulting a third author.

### **3.11 Risk of Bias Assessment**

Following the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins et al., 2019), risk of bias will be assessed across the following domains:

1. Random sequence generation,
2. Allocation concealment,
3. Blinding of participants and personnel,
4. Blinding of outcome assessors,
5. Incomplete outcome data,
6. Selective reporting,
7. Other potential sources of bias (e.g., baseline imbalances).

Domains 1, 2, 5, and 7 will be assessed at the study level, while domains 3, 4, and 6 may also be assessed at the outcome level if necessary. Two independent authors will make these judgments, providing reasons for each decision. A third author will resolve disagreements.

### **3.12 Measures of Treatment Effect**

All reported time points from the RCTs will be considered. Time points will be pooled into short-term (immediately post-treatment to 1 month), intermediate-term (1–3 months), and long-term (>3 months) intervals.

### **3.13 Subgroup or Subset Analyses**

Data will be analyzed separately for subgroups including age groups (young adults vs. older adults), ulcer stages (acute vs. chronic), and patients with or without diabetes.

RCTs with a high risk of bias will be excluded from the meta-analysis to ensure sensitivity and reliability.

### 3.14 Strategy for Data Synthesis

The individual participant will be considered as the unit of analysis. Mean differences (MD) for continuous outcomes and risk ratios (RR) for dichotomous outcomes (with a 95% confidence interval) will be calculated. Where data availability and homogeneity permit, treatment effects will be combined using a random-effects model meta-analysis in Review Manager 5.4.1. Heterogeneity will be assessed by visual inspection of forest plots, the Chi<sup>2</sup> test ( $p > 0.1$  indicating statistical heterogeneity), and the I<sup>2</sup> statistic (I<sup>2</sup> > 50% indicating significant inconsistency).

### 3.15 Assessment of the Certainty of Evidence

The certainty of the body of evidence was assessed using the GRADE approach (Grading of Recommendations Assessment, Development, and Evaluation Working Group) (Guyatt et al., 2008). This approach evaluates five domains (methodological limitations, inconsistency, imprecision, indirect evidence, and publication bias) and categorizes evidence as low, low, moderate, or high certainty. A summary of findings and reasons for downgrading evidence certainty were presented. While study design indicates evidence quality, other criteria, such as factors that decrease or increase evidence quality, were also considered (Tables 1, 2, and 3).

**Table 2 – Factors Related to the Initial Quality of Evidence**

<b>Study Type</b>	<b>Initial Evidence Quality</b>
Randomized Studies	High quality
Observational Studies	Low quality

Source: (Saúde/; Fiocruz, 2013)

**Table 3 – Factors That Decrease the Quality of Evidence**

<b>Topic</b>	<b>Definition</b>
<b>Methodological Limitations</b>	- Inadequate randomization
	- Lack of blinding
	- Absence of intention-to-treat analysis
	- Follow-up losses
	- Early trial termination due to benefits

<b>Topic</b>	<b>Definition</b>
<b>Inconsistency</b>	Heterogeneity among studies, preferably indicated by the Higgs inconsistency percentage test.
<b>Indirect Evidence</b>	The available studies do not directly answer the issue being addressed due to differences in population, interventions, comparators, or outcomes.
<b>Imprecision</b>	Wide confidence intervals indicate uncertainty about the true effect of the intervention.
<b>Publication Bias</b>	Tendency to publish studies with positive results, especially in English and in journals indexed in MEDLINE. The exclusive availability of small studies suggests a higher risk of publication bias.

Fonte: (SAÚDE/; FIOCRUZ, 2013)

**Table 4 – Factors That Increase the Quality of Evidence**

<b>Topic</b>	<b>Definition</b>
<b>Large Magnitude of Effect</b>	When the magnitude of the effect estimate is very large, it becomes less likely that potential confounders explain the observed effect.
<b>Confounders Leading to Underestimation</b>	There are situations where confounders and other biases act to reduce the effect estimate.
<b>Dose-Response Gradient</b>	The presence of a dose-response gradient increases confidence in the estimates of observational studies.

Source: (Saúde/; Fiocruz, 2013)

### 3.16 Data Analysis

Meta-analysis based on the weighted mean difference was conducted for selected dichotomous outcomes. Results were reported with the corresponding 95% confidence intervals (CI 95%). Calculations were performed using the R software (The R Foundation for Statistical Computing, Austria). For all analyses, the significance level was set at  $p < 0.05$ .

**Data availability Statement-** all data will be available for the readers.

**Dissemination policy:** All data share trial results with participants, healthcare professionals, the public, and relevant groups.

**Review protocol:** the review protocol was registered in PROSPERO: CRD42023412304

**Disclaimer (Artificial intelligence):** Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

## REFERENCES

1. Zaidi SRH, Sharma S. Pressure Ulcer. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. PMID: 31971747. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK553107/>
2. Li Z, Lin F, Thalib L, Chaboyer W. Global prevalence and incidence of pressure injuries in hospitalised adult patients: A systematic review and meta-analysis. *Int J Nurs Stud*. 2020;105:103546. doi:10.1016/j.ijnurstu.2020.103546
3. Tubaishat A, Papanikolaou P, Anthony D, Habiballah L. Pressure ulcers prevalence in the acute care setting: a systematic review, 2000-2015. *Clin Nurs Res*. 2018;27(6):643-59. doi:10.1177/1054773817705541
4. Van Den Bos J, Rustagi K, Gray T, Halford M, Ziemkiewicz E, Shreve J. The \$17.1 billion problem: the annual cost of measurable medical errors. *Health Aff (Millwood)*. 2011 Apr;30(4):596-603. doi:10.1377/hlthaff.2011.0084
5. Brem H, Maggi J, Nierman D, Rolnitzky L, Bell D, Rennert R, et al. High cost of stage IV pressure ulcers. *Am J Surg*. 2010 Oct;200(4):473-7. doi:10.1016/j.amjsurg.2009.12.021
6. Edsberg LE, Black JM, Goldberg M, McNichol L, Moore L, Sieggreen M. Revised National Pressure Ulcer Advisory Panel pressure injury staging system. *J Wound Ostomy Continence Nurs*. 2016;43(6):585-97. doi:10.1097/WON.0000000000000281
7. Salgado LP, Rocha DC, Costa AC, Santana PM, Lima MA. Escalas preditivas utilizadas por enfermeiros na prevenção de lesão por pressão. *Rev Saber Digital*. 2018;11(1):18-35. Available from: <https://revistas.faa.edu.br/SaberDigital/article/view/468/349>
8. Reddy M. Pressure ulcers: treatment. *BMJ Clin Evid*. 2015 Dec 11;2015:1901. PMID: 26666978; PMCID: PMC4678418
9. Gushiken LFS, Beserra FP, Bastos JK, Jackson CJ, Pellizzon CH. Cutaneous wound healing: An update from physiopathology to current therapies. *Life (Basel)*. 2021;11(7):665. doi:10.3390/life11070665
10. Andrade FS, Clark RM, Ferreira ML. Efeitos da laserterapia de baixa potência na cicatrização de feridas cutâneas. *Rev Col Bras Cir*. 2014;41(4):262-5. doi:10.1590/0100-69912014004009
11. Freitas LF, Hamblin MR. Photobiomodulation: Some key questions. *J Biophotonics*. 2017;10(11):1455-77. doi:10.1002/jbio.201600229
12. Jana Neto FC, de Souza JB, Ribeiro IM, Grillo C, Reis CP, Sampaio L, et al. Effects of multiwavelength photobiomodulation for the treatment of traumatic soft tissue injuries associated with bone fractures: A double-blind, randomized controlled clinical trial. *J Biophotonics*. 2023;16(5). doi:10.1002/jbio.202200299
13. Petz FFC, Ramos S, Alves JL, Nogueira RD, Machado ACP, Castro IO, et al. Effect of photobiomodulation on repairing pressure ulcers in adult and elderly patients: A systematic review. *Photochem Photobiol*. 2020;96(1):191-9. doi:10.1111/php.13176
14. Higgins JPT, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* [updated March 2011]. The Cochrane Collaboration; 2011. Available from: [www.cochrane-handbook.org](http://www.cochrane-handbook.org).

15. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6(7). doi:10.1371/journal.pmed.1000097.
16. PROSPERO [Internet]. International Prospective Register of Systematic Reviews. University of York Centre for Reviews and Dissemination. Available from: <https://www.crd.york.ac.uk/prospero/>
17. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ.* 2008;336(7650):924-6. doi:10.1136/bmj.39489.470347.AD

UNDER PEER REVIEW