Journal of Advances in Medicine and Medical Research

Volume 36, Issue 12, Page 212-218, 2024; Article no.JAMMR.127582
ISSN: 2456-8899, NLM ID: 101711724
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Efficacy and Safety of Photobiomodulation on Non-infected Pressure Ulcer in Adults: A Study Protocol of Randomized Clinical Trials

Adriana da Silva Magalhães [a], Lara Jansiski Motta [a], Isabel Veloso Alves Pereira [b], Sandra Kalil Bussadori [a,c], Cinthya Cosme Gutierrez Duran [a], Kristianne Porta Santos Fernandes [a], Raquel Agnelli Mesquita-Ferrari [a,c] and Anna Carolina Ratto Tempestini Horliana [a*]

[a] Postgraduate Program in Biophotonics-Medicine, Universidade Nove de Julho (UNINOVE), São Paulo, Brazil
[b] Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil.
[c] Postgraduate Program in Reabilitation Sciences, Universidade Nove de Julho (UNINOVE), São Paulo, Brazil.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: https://doi.org/10.9734/jammr/2024/v36i125668

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/127582

Study Protocol

Received: 06/10/2024
Accepted: 08/12/2024
Published: 14/12/2024

**Corresponding author: E-mail: annacrth@gmail.com;*

Cite as: *Magalhães, Adriana da Silva, Lara Jansiski Motta, Isabel Veloso Alves Pereira, Sandra Kalil Bussadori, Cinthya Cosme Gutierrez Duran, Kristianne Porta Santos Fernandes, Raquel Agnelli Mesquita-Ferrari, and Anna Carolina Ratto Tempestini Horliana. 2024. "Efficacy and Safety of Photobiomodulation on Non-Infected Pressure Ulcer in Adults: A Study Protocol of Randomized Clinical Trials". Journal of Advances in Medicine and Medical Research 36 (12):212-18. https://doi.org/10.9734/jammr/2024/v36i125668.*

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.

1. 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% (Pearson et al., 2000) to 18.5% (Gallagher et al., 2008). Treating hospital-acquired pressure injuries represents a significant financial burden for healthcare systems. In 2008, the estimated annual cost of measurable medical errors causing harm to patients was $17.1 billion, with pressure ulcers identified as the most common error (Van Den Bos, 2011).

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.

2. METHODS

2.1 Study Design

This study 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.

2.2 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.

2.3 Review Question

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

2.4 Types of Studies to Be Included

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

2.5 Population

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

2.6 Intervention

Photobiomodulation using LED or laser at any wavelength.

2.7 Comparator

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

2.8 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.

2.9 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.

2.10 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.

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)

2.11 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.

2.12 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.

2.13 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.

2.14 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^2 test ($p > 0.1$ indicating statistical heterogeneity), and the I^2 statistic ($I^2 > 50\%$ indicating significant inconsistency).

2.15 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 2, 3, and 4).

2.16 Data Analysis

Meta-analysis based on the weighted mean difference was conducted for selected dichotomous outcomes. Results were reported with the corresponding 95% confidence

Table 2. Factors related to the initial quality of evidence

Study Type	Initial Evidence Quality
Randomized Studies	High quality
Observational Studies	Low quality

Source: (Saúde/; Fiocruz, 2013)

Table 3. Factors that decrease the quality of evidence

Topic	Definition
Methodological Limitations	- Inadequate randomization - Lack of blinding - Absence of intention-to-treat analysis - Follow-up losses - Early trial termination due to benefits
Inconsistency	Heterogeneity among studies, preferably indicated by the Higgs inconsistency percentage test.
Indirect Evidence	The available studies do not directly answer the issue being addressed due to differences in population, interventions, comparators, or outcomes.
Imprecision	Wide confidence intervals indicate uncertainty about the true effect of the intervention.
Publication Bias	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

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

Source: (Saúde/; Fiocruz, 2013)

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.

3. DISCUSSION

The methods proposed in this systematic review protocol adhere to the widely recognized guidelines of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2011) and the PRISMA Statement (Moher et al., 2009). This methodological approach ensures transparency, rigor, and reproducibility in the collection, analysis, and synthesis of data. By including a comprehensive search in indexed databases and gray literature, the protocol minimizes publication bias and increases the likelihood of identifying all relevant studies (Li et al., 2020). Using the PICO framework to define the research question is a strength, as it allows for a targeted and thorough selection of studies addressing the efficacy and safety of photobiomodulation in treating non-infected pressure ulcers. Furthermore, including randomized controlled trials (RCTs) with a parallel design contributes to the quality of evidence, as these studies are considered the gold standard for evaluating therapeutic interventions (Guyatt et al., 2008). The protocol carefully addresses potential biases through robust risk assessment tools, such as the criteria outlined in the Cochrane Handbook (Higgins et al., 2019). Subgroup analyses will enable the evaluation of potential differences in treatment effects among specific populations, such as older adults or patients with diabetes, which may have significant clinical implications (Petz et al., 2020). However, some limitations can be anticipated. First, heterogeneity among included studies, especially regarding intervention characteristics (e.g., photobiomodulation parameters such as wavelength and dose), may pose challenges to an integrated meta-analysis (Freitas & Hamblin,

2017). Additionally, variability in reported outcomes, such as the use of different scales for pain and quality of life, may limit direct comparability across studies (Tubaishat et al., 2018). Finally, excluding studies with a high risk of bias may reduce the total number of studies available for analysis, but it is essential to ensure the validity of the conclusions (Guyatt et al., 2008). Despite these limitations, the protocol provides a robust foundation for evaluating the efficacy and safety of photobiomodulation in pressure ulcers. The results of this systematic review may contribute to evidence-based clinical practice and guide future research in this promising field.

4. CONCLUSION

This systematic review protocol establishes a solid methodological foundation to evaluate the efficacy and safety of photobiomodulation for treating non-infected pressure ulcers in adults. By adhering to the guidelines of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins et al., 2011) and the PRISMA Statement (Moher et al., 2009), the study aims to ensure rigor and transparency in its conduct and analysis. The findings of this review are expected to provide robust evidence to inform clinical practices and healthcare policies, as well as to identify gaps in knowledge that future research can address (Zaidi & Sharma, 2023). Additionally, the results may contribute to the implementation of evidence-based therapies, improving patients' quality of life and reducing the financial burden associated with pressure ulcers (Van Den Bos et al., 2011; Brem et al., 2010).

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that generative AI technologies such as Large Language Models, etc have been used during writing or editing of manuscripts. This explanation will include the name, version, model, and source of the generative AI technology and as well as all input prompts provided to the generative AI technology.

Details of the AI usage are given below:

1. I use chat GPT only to correct the English.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

Andrade, F. S., Clark, R. M., & Ferreira, M. L. (2014). Efeitos da laserterapia de baixa potência na cicatrização de feridas cutâneas. *Revista do Colégio Brasileiro de Cirurgiões, 41*(4), 262–265. https://doi.org/10.1590/0100-69912014004009

Brem, H., Maggi, J., Nierman, D., Rolnitzky, L., Bell, D., Rennert, R., et al. (2010). High cost of stage IV pressure ulcers. *American Journal of Surgery, 200*(4), 473–477. https://doi.org/10.1016/j.amjsurg.2009.12.021

Edsberg, L. E., Black, J. M., Goldberg, M., McNichol, L., Moore, L., & Sieggreen, M. (2016). Revised National Pressure Ulcer Advisory Panel pressure injury staging system. *Journal of Wound, Ostomy, and Continence Nursing, 43*(6), 585–597. https://doi.org/10.1097/WON.0000000000000281

Freitas, L. F., & Hamblin, M. R. (2017). Photobiomodulation: Some key questions. *Journal of Biophotonics, 10*(11), 1455–1477. https://doi.org/10.1002/jbio.201600229

Gushiken, L. F. S., Beserra, F. P., Bastos, J. K., Jackson, C. J., & Pellizzon, C. H. (2021). Cutaneous wound healing: An update from physiopathology to current therapies. *Life (Basel), 11*(7), 665. https://doi.org/10.3390/life11070665

Guyatt, G. H., Oxman, A. D., Vist, G. E., Kunz, R., Falck-Ytter, Y., Alonso-Coello, P., et al. (2008). GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. *BMJ, 336*(7650), 924–926. https://doi.org/10.1136/bmj.39489.470347.AD

Higgins, J. P. T., & Green, S. (Eds.). (2011). *Cochrane handbook for systematic reviews of interventions (version 5.1.0)*. The Cochrane Collaboration. Available from https://www.cochrane-handbook.org

Jana Neto, F. C., de Souza, J. B., Ribeiro, I. M., Grillo, C., Reis, C. P., Sampaio, L., et al. (2023). Effects of multiwavelength photobiomodulation for the treatment of traumatic soft tissue injuries associated

with bone fractures: A double-blind, randomized controlled clinical trial. *Journal of Biophotonics, 16*(5). https://doi.org/10.1002/jbio.202200299

Li, Z., Lin, F., Thalib, L., & Chaboyer, W. (2020). Global prevalence and incidence of pressure injuries in hospitalized adult patients: A systematic review and meta-analysis. *International Journal of Nursing Studies, 105*, 103546. https://doi.org/10.1016/j.ijnurstu.2020.103546

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & PRISMA Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med, 6*(7), e1000097. https://doi.org/10.1371/journal.pmed.1000097

Petz, F. F. C., Ramos, S., Alves, J. L., Nogueira, R. D., Machado, A. C. P., Castro, I. O., et al. (2020). Effect of photobiomodulation on repairing pressure ulcers in adult and elderly patients: A systematic review. *Photochemistry and Photobiology, 96*(1), 191–199. https://doi.org/10.1111/php.13176

PROSPERO. (n.d.). *International Prospective Register of Systematic Reviews*. University of York Centre for Reviews and Dissemination. Available from https://www.crd.york.ac.uk/prospero

Reddy, M. (2015). Pressure ulcers: Treatment. *BMJ Clinical Evidence, 2015*, 1901. PMID: 26666978; PMCID: PMC4678418

Salgado, L. P., Rocha, D. C., Costa, A. C., Santana, P. M., & Lima, M. A. (2018). Escalas preditivas utilizadas por enfermeiros na prevenção de lesão por pressão. *Revista Saber Digital, 11*(1), 18–35. Available from https://revistas.faa.edu.br/SaberDigital/article/view/468/349

Tubaishat, A., Papanikolaou, P., Anthony, D., & Habiballah, L. (2018). Pressure ulcers prevalence in the acute care setting: A systematic review, 2000–2015. *Clinical Nursing Research, 27*(6), 643–659. https://doi.org/10.1177/1054773817705541

Van Den Bos, J., Rustagi, K., Gray, T., Halford, M., Ziemkiewicz, E., & Shreve, J. (2011). The $17.1 billion problem: The annual cost of measurable medical errors. *Health Affairs (Millwood), 30*(4), 596–603. https://doi.org/10.1377/hlthaff.2011.0084

Zaidi, S. R. H., & Sharma, S. (2023). *Pressure ulcer*. In *StatPearls* [Internet]. StatPearls Publishing. Available from https://www.ncbi.nlm.nih.gov/books/NBK553107/

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of the publisher and/or the editor(s). This publisher and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.

© Copyright (2024): Author(s). The licensee is the journal publisher. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/127582