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A meta-analysis on the use of photobiomodulation to regulate gingival wound healing in addition to periodontal therapies

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Abstract
Background:
A meta-analysis research was implemented to appraise gingival wound healing management by photobiomodulation as adjunctive management to periodontal treatments.
Inclusive literature research till April 2023 was done and 908 interconnected researches were revised. Methods
The 9 picked researches, enclosed 517 periodontal disease persons were in the utilized researchers' starting point, 258 of them were utilizing photobiomodulation, and 259 were control. Odds ratio (OR) and 95% confidence intervals (CIs) were utilized to appraise the consequence of photobiomodulation in treating gingival wound healing by the dichotomous, and contentious approach and a fixed or random model.
Results:
Photobiomodulation had a significantly higher Landry wound healing index (MD, 0.87; 95% CI, 0.40-1.34, p<0.001), and complete wound epithelialization (OR, 6.47; 95% CI, 2.05-20.44, p=0.001) compared to the control of gingival wound healing in periodontal disease persons. However, photobiomodulation and control had no significant difference in the remaining wound area (MD, -10.03; 95% CI, -22.83-2.77, p=0.12) of gingival wound healing in periodontal disease persons.
Conclusions:
Photobiomodulation had a significantly higher Landry wound healing index, and complete wound epithelialization, however, no significant difference was found in the remaining wound area compared to control of gingival wound healing in periodontal disease persons. However, caution needs to be taken when interacting with its values since there was a low sample size of most of the chosen research found for the comparisons in the meta-analysis and a low number of chosen investigations for some of the comparisons.
Keywords: complete wound epithelialization; photobiomodulation; periodontal disease; remaining wound area of the wound; Landry wound healing index

Introduction

Enhancing wound healing following periodontal surgery is essential for obtaining positive clinical outcomes. [1] Better periodontal treatment outcomes and patient satisfaction are produced by best wound healing and a decrease in the intensity and period of postoperative pain. [2] Sometimes delayed wound healing is linked to a feeling of postoperative discomfort or pain. [3] It is affected by a number of psychological, clinical, and iatrogenic factors, comprising stress and psychological health, prior experiences of the patient, the type and length of surgery, the experience and skills of the surgeon, and the method of wound closure. [4] Applying chlorhexidine with or without alcohol, [5] dietary supplements, [6] antibiotics like azithromycin, [7] vitamin D, [8] professional teeth cleaning, [9] and the usage of fibrin sealants rather than sutures [10] are a few of the common drugs and treatments utilized by clinicians to speed wound healing following periodontal surgeries. After periodontal flap procedures, secondary intention healing wounds may cause more discomfort and take longer to heal than primary intention healing wounds. Common secondary intention healing wounds include gingivectomies, depigmentation treatments, and extracting free gingival graft tissues from the palatal region. This kind of wound healing happens when the wound site is left untreated, allowing granulation, contraction, and epithelialization to take place. Additionally, we see greater contraction and scar development. [11] Numerous researchers have been released recently about the usage of photobiomodulation as adjuvant management to enhance wound healing. [12] In photobiomodulation, laser or light-emitting diode beams are utilized to stimulate healing, alleviate pain, and reduce inflammation. [13] The feasibility and proliferation of skin and gingival fibroblast cells have been demonstrated to be positively induced by photobiomodulation. [12] As a result, this biophysical approach has been taken into consideration as a therapeutic method that can promote the body's natural healing process. The primary hypotheses for the biological response that has been observed include the absorption of low-level light by cellular photoreceptors, the manufacture of the succeeding generation of highly reactive, transient biochemical intermediates, variations in cellular ionic gradients or cell polarity, and an increase in ATP manufacture, transcription factor usage, and cell activity. This causes a secondary phase of reactions, which promotes wound healing by promoting angiogenesis, cell proliferation, differentiation, and migration, as well as the generation of growth factors and matrix synthesis. [14] Photobiomodulation reduces pain perception, promotes keratinization, and improves periodontal clinical features such as probing depth and clinical attachment level. [15] Although there are some questions about the reported outcomes, several investigations have shown the significant impact of photobiomodulation on postoperative pain decrease and wound healing improvement subsequent to periodontal procedures. [16] To acquire an optimal dose of irradiation, it is crucial to take into account the characteristics of the photobiomodulation irradiation parameters, as too little or too much radiation may have no consequence or unfavorable inhibitory effects on wound healing. [17] There is a great knowledge of the usage of photobiomodulation in the field of wound healing, and several laser wavelengths and settings have been utilized to improve oral wound healing. The effects on open soft tissue wounds in the mouth and the best laser qualities to speed up the healing of these wounds have not yet been determined. In order to find an evidence-based response to the question "Does the application of photobiomodulation as an adjunct therapy, improve the secondary intention wound healing after periodontal soft tissue surgeries?" This meta-analysis aimed to appraise gingival wound healing management by photobiomodulation as adjunctive management to periodontal treatments.

Methods

Eligibility criteria

The research demonstrating gingival wound healing management by photobiomodulation as adjunctive management to periodontal treatments was selected in order to create an overview. [18]

Information sources

The entire research is represented in Figure 1. The literature was inserted into the research when the inclusion criteria were met:

1. The investigation was observational, prospective, retrospective, or randomized controlled trial (RCT) research.
2. Persons with periodontal disease were investigated picked persons.
3. The intervention was photobiomodulation.
4. The research appraised the outcome of the gingival wound healing management by photobiomodulation as adjunctive management to periodontal treatments

The research was excluded if the comparison significance was not emphasized in it, research that didn't check the characteristics of the consequence of the gingival wound healing management by photobiomodulation as adjunctive management to periodontal treatments, and research on gingival wound healing management in persons without using photobiomodulation.

Search strategy

A search protocol operations were recognized based on the PICOS view, and we characterized it as next: "population" for persons with periodontal disease, P; photobiomodulation is the "intervention" or "exposure," while the "comparison" was between photobiomodulation and control; Landry wound healing index, complete wound epithelialization, and remaining wound area of the wound was the "outcome" and, "research design" the planned research had no boundaries. [19]

We have searched Google Scholar, Embase, Cochrane Library, PubMed, and OVID databases thoroughly till April 2023 utilizing an organization of keywords and supplementary keywords for complete wound epithelialization; photobiomodulation; periodontal disease; remaining wound area of the wound; and Landry wound healing index as revealed in Table 1. To evade an investigation from being unsuccessful to create a connection between the effects of gingival wound healing management by photobiomodulation as adjunctive management to periodontal treatments, paper replications were removed, they were grouped into an EndNote file, and the titles and abstracts were reevaluated.

Selection process

The procedure that followed the epidemiological declaration was later organized and analyzed utilizing the meta-analysis method.

Data collection process

The first author's name, the research data, the research year, the country or area, the population kind, the medical and treatment physiognomies, categories, the quantitative and qualitative estimation procedure, the data source, the outcome estimation, and statistical analysis were some of the criteria utilized to collect data. [20]

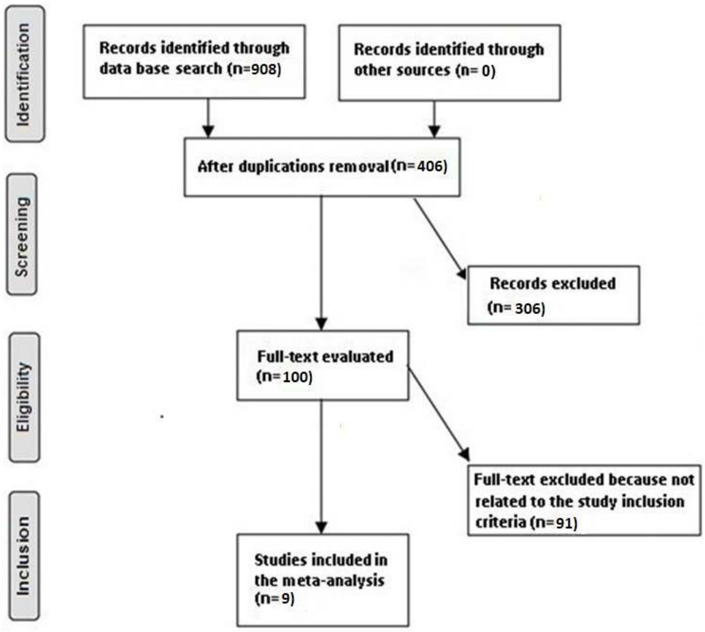

Figure 1 A flowchart of the research process.

Table 1. Search Strategy for Each Database

Database	Search strategy
Pubmed	#1 "complete wound epithelialization"[MeSH Terms] OR "Landry wound healing index"[MeSH Terms] [All Fields] #2 " remaining wound area of the wound"[MeSH Terms] OR "photobiomodulation"[MeSH Terms] OR "periodontal disease"[MeSH Terms] [All Fields] #3 #1 AND #2
Embase	'complete wound epithelialization'/exp OR 'Landry wound healing index' #2 'remaining wound area of the wound '/exp OR 'photobiomodulation'/exp OR 'periodontal disease' #3 #1 AND #2
Cochrane library	(complete wound epithelialization) :ti,ab,kw (Landry wound healing index):ti,ab,kw (Word variations have been searched) #2 (remaining wound area of the wound):ti,ab,kw OR (photobiomodulation):ti,ab,kw OR (periodontal disease):ti,ab,kw (Word variations have been searched) #3 #1 AND #2

Data items

We separately collected the data based on an assessment of the consequence of photobiomodulation compared to control on gingival wound healing in periodontal disease on Landry wound healing index, complete wound epithelialization, and remaining wound area when research had varying values.

Research risk of bias assessment

To determine whether each research may have been biased, the author independently appraised the methodology of the picked articles. The "risk of bias instrument" from the Cochrane Handbook for Systematic Reviews of

Interventions Version 5.1.0 was utilized to measure procedural quality. Each research was assigned one of the following bias risks after being categorized by the appraisal criteria: If all of the quality requirements were met, the research was classified as having a low bias risk; if one requirement wasn't met or wasn't encompassed, research was classified as having a medium bias risk. If more than one quality requirements were wholly or partially unmet, the research was assessed to have a considerable bias risk.

Effect estimates

Only research that estimated and described the effect of photobiomodulation compared to control on gingival wound healing in periodontal disease underwent sensitivity analysis. To compare photobiomodulation to control on gingival wound healing in periodontal disease persons' sensitivity, a subclass analysis was utilized.

Synthesis methods

The odds ratio (OR) and a 95% confidence interval (CI) were calculated utilizing a random- or fixed-effect model and a dichotomous, and contentious approach. The I2 index was calculated between 0 and 100%. No, low, moderate, and high heterogeneity were evident for the values at 0%, 25%, 50%, and 75%, respectively. [21] Other structures that display a strong degree of alikeness among the connected investigation were also analyzed to be confident the precise model was utilized. When I2 was 50% or higher, the random effect was employed; if I2 was <50%, the option of utilizing fixed-effect rose. [21] By dividing the initial estimation into the aforementioned consequence groups, a subclass analysis was carried out. In order to define the statistical significance of differences among subcategories, a p-value of less than 0.05 was utilized in the analysis.

Reporting bias assessment

The Egger regression test and funnel plots that show the logarithm of the ORs vs. their standard errors were utilized to quantitatively and qualitatively quantify investigation bias. Investigations bias was declared present if p≥0.05.[22]

Certainty assessment

Each p-value was inspected utilizing two-tailed testing. Utilizing Reviewer Manager Version 5.3, graphs and statistical analyses were created (The Nordic Cochrane Centre, the Cochrane Collaboration, Copenhagen, Denmark).

Results

9 papers, published between 2008 and 2023, from a total of 908 linked research that met the inclusion criteria were chosen for the research. [23-31] The consequences of these investigations are accessible in Table 2. 517 periodontal disease persons were in the utilized researchers' starting point, 258 of them were utilizing photobiomodulation, and 259 were control. The sample size was 20 to 240 persons.

Photobiomodulation had a significantly higher Landry wound healing index (MD, 0.87; 95% CI, 0.40-1.34, p<0.001) with high heterogeneity (I^2 = 96%), and complete wound epithelialization (OR, 6.47; 95% CI, 2.05-20.44, p=0.001) with no heterogeneity (I^2 = 0%) compared to control of gingival wound healing in periodontal disease persons as revealed in Figures 2 & 3. However, photobiomodulation and control had no significant difference in the remaining wound area (MD, -10.03; 95% CI, -22.83-2.77, p=0.12) with high heterogeneity (I^2 = 84%) of gingival wound healing in periodontal disease persons as revealed in Figure 4.

The utilization of stratified models to examine the effects of specific components was not possible due to a lack of data, e.g. age, gender, and ethnicity, on comparison outcomes. No evidence of research bias was found (p = 0.87) operating the quantitative Egger regression test and the visual interpretation of the funnel plot as shown in Figures 5-7. Though, it was discovered that the mainstream of the implicated RCTs had poor procedural quality and no bias in selective reporting.

Table 2. Characteristics of the selected researches for the meta-analysis

Investigation	Country	Total	photobiomodulation	Control
Ozcelik, 2008 [23]	Turkey	20	10	10
Ustaoglu, 2017 [24]	Turkey	35	17	18
Heidari, 2017 [25]	Iran	24	12	12
Kohale, 2018 [26]	India	88	44	44
Isler, 2018 [27]	Turkey	24	12	12
Lingamaneni, 2019 [28]	India	20	10	10
Morshedzadeh, 2022 [29]	Iran	28	14	14
Bozkurt, 2022 [30]	Turkey	38	19	19
Misra, 2023 [31]	India	240	120	120
	Total	**517**	**258**	**259**

Study or Subgroup	Photobiomodulation Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Ustaoglu, 2017	4	0.58	17	3	0.29	18	16.9%	1.00 [0.69, 1.31]	2017
Kohale, 2018	3.35	0.48	44	2.85	0.36	44	17.7%	0.50 [0.32, 0.68]	2018
Isler, 2018	2.02	0.34	12	1.83	0.37	12	17.1%	0.19 [-0.09, 0.47]	2018
Lingamaneni, 2019	4.1	0.567	10	3.5	0.971	10	13.0%	0.60 [-0.10, 1.30]	2019
Bozkurt, 2022	3	0.33	19	1.16	0.37	19	17.5%	1.84 [1.62, 2.06]	2022
Misra, 2023	3.5	0.67	120	2.5	0.5	120	17.9%	1.00 [0.85, 1.15]	2023
Total (95% CI)			222			223	100.0%	0.87 [0.40, 1.34]	

Heterogeneity: $Tau^2 = 0.31$; $Chi^2 = 114.48$, df = 5 ($P < 0.00001$); $I^2 = 96\%$
Test for overall effect: Z = 3.64 (P = 0.0003)

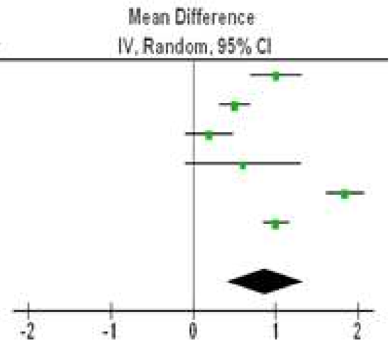

Figure 2. The effect's forest plot of the photobiomodulation compared to control on Landry wound healing index in gingival wound healing in periodontal disease

Study or Subgroup	Photobiomodulation Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Heidari, 2017	3	12	0	12	14.3%	9.21 [0.42, 200.59]	2017
Bozkurt, 2022	14	19	7	19	72.0%	4.80 [1.20, 19.13]	2022
Morshedzadeh, 2022	14	14	10	14	13.7%	12.43 [0.60, 256.66]	2022
Total (95% CI)		**45**		**45**	**100.0%**	**6.47 [2.05, 20.44]**	
Total events	31		17				

Heterogeneity: $Chi^2 = 0.41$, df = 2 ($P = 0.82$); $I^2 = 0\%$
Test for overall effect: Z = 3.18 (P = 0.001)

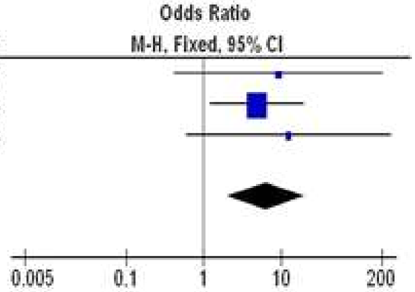

Figure 3. The effect's forest plot of the photobiomodulation compared to complete wound epithelialization of the wound in gingival wound healing in periodontal disease

Study or Subgroup	Photobiomodulation Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Ozcelik, 2008	0.61	0.67	10	1.02	0.78	10	43.7%	-0.41 [-1.05, 0.23]	2008
Isler, 2018	36.04	9.66	12	48.21	13.2	12	35.6%	-12.17 [-21.42, -2.92]	2018
Morshedzadeh, 2022	85.05	27.88	14	111.74	27.32	14	20.7%	-26.69 [-47.14, -6.24]	2022
Total (95% CI)			36			36	100.0%	-10.03 [-22.83, 2.77]	

Heterogeneity: $Tau^2 = 97.50$; $Chi^2 = 12.49$, df = 2 ($P = 0.002$); $I^2 = 84\%$
Test for overall effect: Z = 1.54 (P = 0.12)

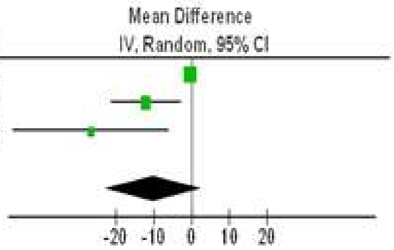

Figure 4. The effect's forest plot of the photobiomodulation compared to remaining wound area of the wound in gingival wound healing in periodontal disease

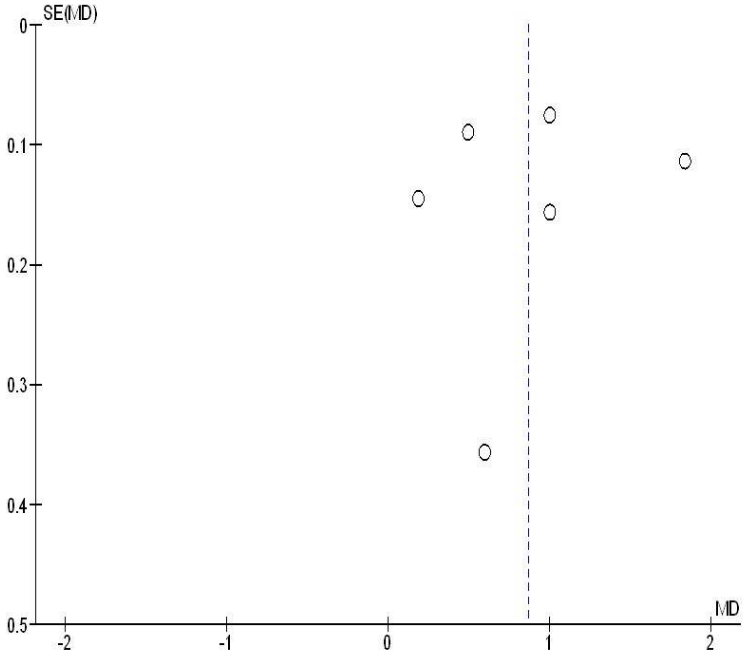

Figure 5. The funnel plot of the photobiomodulation compared to control on Landry wound healing index in gingival wound healing in periodontal disease

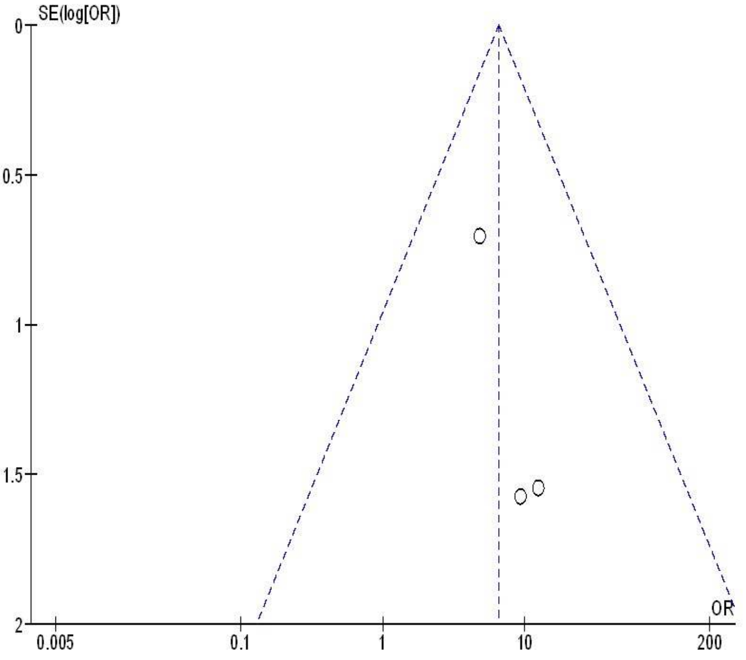

Figure 6. The funnel plot of the photobiomodulation compared to control on Landry wound healing index in gingival wound healing in periodontal disease

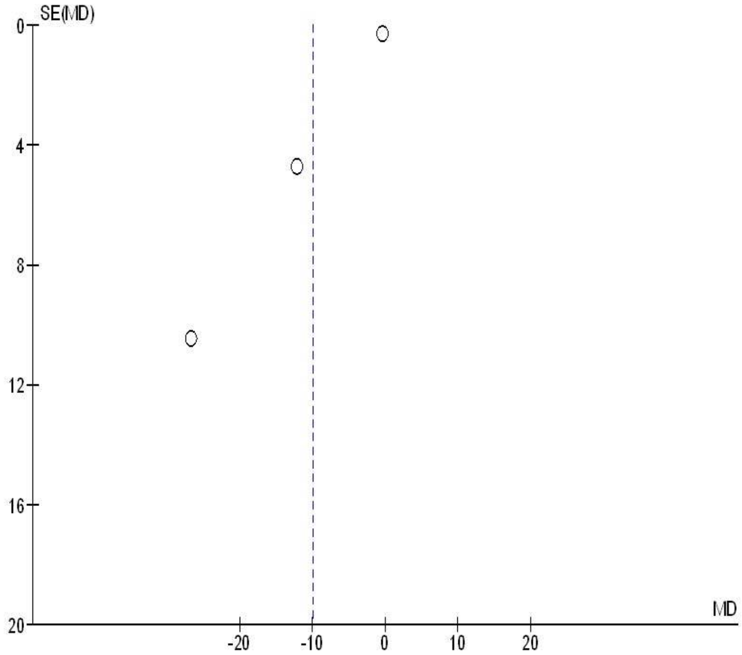

Figure 7. The funnel plot of the photobiomodulation compared to remaining wound area of the wound in gingival wound healing in periodontal disease

Discussion

In the research that was utilized for the meta-analysis, 517 periodontal disease persons were in the utilized researchers' starting point, 258 of them were utilizing photobiomodulation, and 259 were control. [23-31] Photobiomodulation had a significantly higher Landry wound healing index, and complete wound epithelialization compared to control of gingival wound healing in periodontal disease persons. However, photobiomodulation and control had no significant difference in the remaining wound area of gingival wound healing in periodontal disease persons. However, when interacting with its values, caution must be taken since a low sample size of most of the chosen researchers was found for the comparisons in the meta-analysis (8 out of 9 <100 persons) and the low number of chosen investigations for some of the comparisons. The degree of relevance of the evaluation would be impacted by that.

Despite the therapeutic success of photobiomodulation, there are several, sometimes opposing views regarding the precise mechanisms causing better clinical results. The most well-known and traditional theory that has lately come under scrutiny [32] is that red-to-near-infrared photons are absorbed by cytochrome c oxidase chromophores in the mitochondria of cellules, which play a crucial role in the interaction between photons and cells. The electrons in chromophores are stimulated during the absorption process, which results in a proton gradient and, ultimately, a rise in ATP and glycolysis, which in turn leads to increased cellular proliferation and differentiation. [14] Numerous research have suggested that photobiomodulation may speed up and improve the quality of wound healing, and various processes have been looked into. Interleukin-8 levels, platelet-derived growth factor-BB, transforming growth factor-b1, and palatal wound fluid levels all rose, according to Keskiner et al. This could mean that the secretion of particular mediators has been stimulated, which would accelerate the rate of wound healing. [33] There have also been reports of enhanced collagen formation, elevated levels of growth factors and proteins that remodel the extracellular matrix, accelerated adenosine triphosphate synthesis, fibroblastic proliferation, and angiogenesis in a dose-dependent manner. [12, 24-26] Improvements in the wound healing process may have a direct impact on pain reduction, reepithelialization, and tissue thickness. The mechanism and impact of photobiomodulation on primary or secondary wound healing may differ noticeably, according to a recent meta-analysis. [34] This might be because secondary and primary wound healing involves various cellular and molecular processes and healing mechanisms. In the proliferation stage of wound healing, secondary healing entails increased granulation and collagenous tissue production, as well as increased remodeling and contraction. Additionally, secondary healing creates more scar tissue at the wound site and is linked to an increased risk of wound infection. [11] Therefore, the usage of photobiomodulation in these patients may be more advantageous. Only the consequence of photobiomodulation on secondary intention healing gingival wounds has been examined in this investigation. Despite the fact that all of the investigations comprised in the current meta-analysis utilized irradiation wavelengths in the red and near-infrared range, they revealed a great difference in irradiation parameters and the application technique of the adjunctive photobiomodulation management, making it difficult to draw conclusions depending on evidence about the best irradiation settings required for improving healing and pain relief. Due to the wide range of irradiation parameters

seen in the literature currently available, the optimal laser settings for biostimulation of healing and decrease of postoperative pain of periodontal surgical wounds have not yet been identified. In the usage of lasers, variables like the fiber's width can change the power density and energy output. Additionally, it might modify the amount of energy utilized during the procedure, changing how photobiomodulation affects how quickly wounds heal. The included research utilized a range of irradiation settings and wavelengths to photobiomodulate the wounds. One investigation performed photobiomodulation using a neodymium-doped yttrium aluminum garnet laser (1084 nm) device, which had beneficial influences on healing. Only one investigation employed a light-emitting diode 650 nm device, showing favorable results on both wound healing and postoperative discomfort. The surgical sites were illuminated in the other included trials using diode lasers with red to near-infrared wavelengths (588-970 nm). The range of energy densities was 1.6 to 8.6 J/cm2. 4 J/cm2 per point was utilized as the energy density in the majority of research. The output powers, however, ranged from 0.05 to 5 W.
This meta-analysis presented gingival wound healing management by photobiomodulation as adjunctive management to periodontal treatments. More examination is still necessary to illuminate these possible impacts. This was similarly emphasized in former research that utilized a connected meta-analysis practice and originated comparable values of the impact. [35, 36] Though the meta-analysis was unable to determine if differences in these variables are connected to the research results, properly-led RCTs must take these factors into account in addition to the variety of diverse ages, gender, and ethnicities of people. In conclusion, photobiomodulation had significantly higher Landry wound healing index, and complete wound epithelialization compared to control of gingival wound healing in periodontal disease persons. However, photobiomodulation and control had no significant difference in the remaining wound area of gingival wound healing in periodontal disease persons.

Limitations

There might have been assortment bias since several of the researchers chosen for the meta-analysis were excluded. Though, the removed research did not encounter the requirements for inclusion in the meta-analysis. Furthermore, we lacked the knowledge to assess whether parameters like age, gender, and ethnicity affected outcomes. The goal of the research was to determine how photobiomodulation and control will affect Landry wound healing index, complete wound epithelialization, and remaining wound area for gingival wound healing management of the periodontal disease. Due to the inclusion of inaccurate or missing data from previous research, bias might have been amplified. The persons' nutritional state in addition to their race, gender, and age were probable causes of bias. Inadvertently distorted values may result from missing data and some unpublished work.

Conclusions

Photobiomodulation had significantly higher Landry wound healing index, and complete wound epithelialization compared to control of gingival wound healing in periodontal disease persons. However, photobiomodulation and control had no significant difference in the remaining wound area of gingival wound healing in periodontal disease persons. However, when interacting with its values, caution must be taken since a low sample size of most of the chosen researchers was found for the comparisons in the meta-analysis (8 out of 9 <100 persons) and the low number of chosen investigations for some of the comparisons. The degree of relevance of the evaluation would be impacted by that.

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