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Supplemental Light Therapy in Venous Ulcer Treatment: A Nursing-Focused Protocol Utilizing Outcome-Based Metrics

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Abstract

Venous ulcers are a common sequel of the chronic venous insufficiency and they usually have to be treated over a long term as they heal slowly. Normal treatment usually involves a mixture of topical agents and compression treatment. There is rather limited evidence that low-level laser therapy (LLLT) may be an adjunctive treatment to augment wound healing. The protocol of a randomizing controlled trial (RCT) has been described to evaluate the effectiveness of LLLT as an adjunct to conventional therapy estimated in clinical indicators of the Nursing Outcomes Classification (NOC).The study will involve 40 eligible adults with active venous ulcers in an RCT prospective design. The participants will be randomly selected to either the control group that will go through the regular techniques of wound care or the intervention group that will go through regular care complemented with LLLT. Therapy will be made each week to a maximum 16 weeks or till the ulcer is completely healed. The clinical outcomes will be assessed in terms of 14 NOC indicators of wound healing and tissue integrity which will be rated on a 5-point Likert scale. Lessening of the wound size and scarring are the main outcome measures. The secondary outcomes will be the pain, tissue thickness, and other NOC indicators. The objective of the proposed study is to prove the possibility of LLLT to improve the outcome of healing, shorten terms of treatment and increase the quality of life of patients.The trial applies consistent and validated metrics of analysis in assessing the treatment utility of LLLT as a supplementary measure to standard leg venous ulcer treatment. The results can be added to the evidence-based nursing care and wound management and further implementation of laser treatment in clinics.

Keywords: ***Low-level laser therapy; Venous leg ulcer; Nursing Outcomes Classification; Wound healing; Randomized controlled trial; Nursing intervention; Tissue regeneration; Clinical indicators; Laser-assisted therapy; Chronic wound management.***

1.Introduction

Chronic venous disease is one of the most common diseases of vascular character impacting the global population of people with venous leg ulcers as a major clinical challenge that requires the development of new methods of therapeutic approach. Venous insufficiency is characterized by the difficulty of the hemodynamic changes involving a persistent venous hypertension that prevails and contributes to a deterioration of the microcirculatory location and consequent tissue destruction. This escalating process forms a difficult clinical setting when normal wound healing processes are impaired and further extraordinary measures should be provided in order to gain complete tissue integrity and support the best healing effects. The cost of treating venous ulcers is quite high, and health care sectors of different countries in the world spend much regarding the treatment of the ulcer in addition to the subsequent effects of the recurring events that necessitate the need to treat ulcerations(1).

The venous ulcer development has been identified to be multifactorial with different factors that contribute to their development such as genetic factors, work association, hormonal factors, and comorbidity that further hinder venous returns and reduce tissue perfusion. The interpretation of the interdependencies of these mechanisms necessitates the design of the comprehensive treatment plans that would not only repair the seen symptoms of the tissue damages but combat the pathophysiological mechanisms causing the continuation of the condition. Modern wound management strategies have developed into adopting the use of evidence-based practices to enhance the need to administer the best therapeutic surroundings by the use of superior dressing technologies, plans of action and compression therapy, and some useful interventions to help hasten the process of tissue regeneration.

Photobiomodulation therapy, also known as low-level laser therapy, has become a paradigm shift in wound management systems or strategies, which is a non-invasive form of therapeutic treatment model to tap into the potential of the particular wavelength of light that initiates cellular metabolism and optimizes the tissue repair process. This advanced method of treatment functions under the photochemical and photophysical procedures that trigger different cellular pathways that induce tissue regeneration, inflammation regulation and pain abatement.

The photobiomodulation therapeutic effect is not merely limited to the mechanical stimulation of the tissues as there seem to be complicated molecular responses which act in the form of modulation of the mitochondrion system, adenosine triphosphate synthesis and various cascades of cell signalling, which mediate in enhanced healing(2).

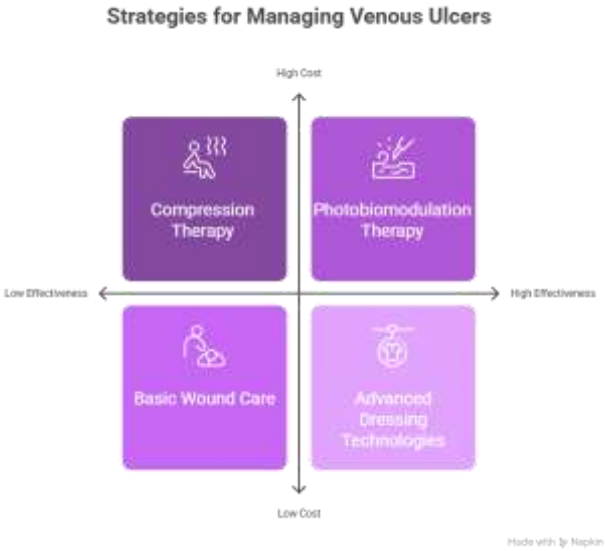

FIGURE 1 Strategies for Managing Venous Ulcers

Existing clinical studies interested in probing into the therapeutic value of photobiomodulation therapy on the management of venous ulcers have shown good responses, albeit the scientific literature unveils a strong degree of variability in the treatment methods, outcome indicators and the methods of investigation. This diversity in research design has presented problems in setting up standardised measures of treatment and has made it clear that more rigorous clinical trial efforts are needed that would use validated tests and multi-faceted outcome measures. Combining the standardized assessing protocols in nursing including those based on Nursing Outcomes Classification system allows establishing an objective system of assessment of the treatment process and deciding in a rational and informed manner on the most effective treatment methods(3).

The importance of this study is not limited to clinical applications only since it can be used to inform the general ideas of how extraordinary modalities of treatment may be combined with current facilities of care delivery to heighten patient outcomes with a possible decrease in the expense of the entire procedure. Evidence-based protocols of photobiomodulation therapy in venous ulcers management are a vital step on the way to enrooting this procedure as a universal part of complex wound care programs, which will positively affect patients by increasing the rate of healing, lowering the level of pain, and improving the outcomes of the quality of life.

2.Review of Literature and Theories

The calculated restrictions on the photobiomodulation therapy in the field of wound healing are based on the same principles of cellular biology and photophysics, which proves how the certain electromagnetic spectrum bands can produce the positive effect of the cellular metabolism and play the role of the tissue regeneration producer due to the presence of strictly determined molecular mechanisms. Substantial research has defined that light in the red and near-infrared frequency band, usually between 660 and 850 nanometers, are the best penetrating tissues and can actively interact with cellular chromophores, especially cytochrome c oxidase that acts as the major photoacceptor in the mitochondrial chain of electron transport. The effect of this interaction is an improved mitochondria respiration, a raised adenosine triphosphate production, and the control of reactive oxygen species production, with this forming a cellular environment that is pro-healing and pro-tissue repair.

Review of the body of literature concerning the applications of the photobiomodulation therapy in the treatment of wounds of different types shows distinctive tendencies of therapeutic advantages such as extraordinary rates of epithelialization, amplification of angiogenesis, ameliorated collagen generation, and diminished pathophysiological responses. Meta-Analysis and systematic reviews have produced strong evidence that low-level laser therapy should be used to treat diabetic ulcers, pressure sores and surgical wounds with large

improvement rates in healing, reduction in wound surface area as well as shortening of time it takes to fully epithelialize wounds. However, the number of studies that considered venous leg ulcers specifically is scarce with the available studies typically having small sample size, mixed treatment regimens and/or outcome measures, which make it difficult to apply to other studies with a wider scope(4).

The very pathophysios of the development of venous ulcers also poses some distinct circumstances that might impact the therapeutic effects on photobiomodulation therapy, and it shall be due to prudent thinking about the factors like the state of tissue oxygenation, the inflammatory state in the reaction, the bacterial colonization and the deposition of fibrin which might affect the penetration of light and reduce the cellular response. Research studying the best parameters of photobiomodulation therapy in the treatment of venous ulcers has to take these variables into consideration and come up with the best methodical protocols in order to boost therapeutic advantage, but not with adverse effects and hampering with existing treatment option like compression and topical wound treatments.

The wound healing theories of today insist on developing balanced levels of inflammation that will lead to a certain repair of the damaged tissues without creating too much scar radioactivity or developing the lengthy periods of the healing time, and photobiomodulation therapy seems to have a role in creating this balance with its modulatory effects on inflammatory mediators and growth factor expression. It has been demonstrated that the right amounts of red light show a drop in the production of pro-inflammatory cytokines but an increase in the production of anti-inflammatory factors to set a more beneficial atmosphere to tissue regeneration. Moreover, the photobiomodulation therapy was found to induce nitric oxide secretion as well as endothelial cell growth and capillary development, which plays essential roles in development of commensurate tissue perfusion within the microenvironment of venous ulcers cited by Colagrande, Martini, Abeni and Orianni, (2014).

When photobiomodulation therapy is incorporated into the general wound care protocols, specific attention should be paid to determining the timing, frequency of treatment sessions and duration of treatment, and also the possible incompatibility with other therapeutic measures aimed at managing the problem of venous ulcers. There are indications that the highest efficacy can be produced when the photobiomodulation therapy is used as an add-on method to the standard wound care procedures and not on its own, which implies the necessity to develop coherent treatment regimens that can take advantage of the synergistic effect of various curative methods so that to deliver the best possible results in terms of wound healing and patient quality of life.

3.Methods

3.1 Design of Study and its Theoretical Framework

This study uses an advanced prospective, well-considered, double-blind, and a randomized controlled trial experimental design that has a specific goal of assessing the therapeutic efficacy of photobiomodulation treatment as an adjunctive treatment to chronic venous leg ulcers. The methodological plan includes recent trends in clinical studies and evidence-based procedures to provide a sound data collection and reduce the effects of confounding factors to provide some credible outcomes that can be used to create clinical practice guidelines. The study protocol is compliant with national standards, introduced by the Consolidated Standards of Reporting Trials (CONSORT) to provide methodological rigor and transparency during each stage of the research process and follows the requirements of the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist to ensure a sufficient level of methodological compliance(5). This research design has a theoretical basis regarding the understanding of the multifactorial nature of the pathophysiology of venous ulcers and a way of accepting that the intervention dealing with therapeutic intervention should be able to interact with multiple biologic pathways. Randomized controlled trial as a research methodology best suits when the particular effects of the therapeutic approach used (photobiomodulation therapy in this case) have to be isolated and placebo effects, investigator bias and time changes in the way wound healing occurs need to be controlled. Parallel-group design allows a direct comparison of an intervention with the control group and considers sufficient statistical power to reach a clinically important difference in primary and secondary outcome variables. The given methodological approach guarantees that the research results will become definitive with respect to the therapeutic utility of the photobiomodulation therapy as the method of managing the venous ulcers and evidence-based clinical decision making.

3.2 Recruitment and Selection of the Participants of the Study

The strategies used to recruit the participants include a detailed screening procedure meant to select people living with chronic venous insufficiency and having active venous leg ulcers who are considered the target group of

beneficiaries of this treatment. The recruitment activities will occur in various ways via outpatient wound care clinics, vascular surgery departments, dermatology practices, and community healthcare centers, and offer a wide range of representation in different demographic groups and varied clinical presentations. The inclusion criteria are also developed in a specific way so that the homogeneity in study population could be achieved on the one hand and the necessary external validity and possibilities to generalize findings on the other hand are also fulfilled. Only eligible participants are adults of 18 years and above who have been diagnosed as having chronic venous insufficiency and has records of such diagnosis that has managed to survive the test of time on its dux and ultrasound, and have an active case of venous leg ulcer scars that are no less than four weeks of clinical administration under the modern method approaches of treatment. Additional criteria of inclusion identify wound characteristics such as; appropriate size parameters (of 2 to 50 cm surface areas), the absence of clinical signs of overt infection, and sufficient arterial response in terms of ankle-brachial index measurements of >0.8. This involves using the screening procedure which encompasses thorough medical history assessment, physical examination, laboratory tests and imaging to ensure the potential participants have all relevant eligibility criteria that make them safe to follow the study procedure. The exclusion criteria are to rule out the issues that may alter the treatment outcomes or make them unsafe, such as advanced peripheral arterial disease, active malignancy, immunosuppressant-based treatment, pregnancy, proven photosensitivity diseases, and even involvement in another clinical trial. Informed consent procedures are the highlights of the recruitment process which provides an explanation to the research participants of the requirements, possible risks and benefits of the study and the rights of the research participants.

3.3 Allocation and Randomizations Procedures

The randomization methodology uses computer-based random sequence allocation constellation system, which aims at assuring the randomness in the assignment of the group during the same balancing interventional group and control groups in demographic and clinical variables. Randomization process employs use of permuted block randomization of varying block sizes to avoid predictability of future assignments and maintain balance Group approximations over time in the recruitment period. To act as a control variable and prevent the distribution of such influential prognostic variables as wound size, duration of ulceration, and age of patients unevenly across the treatment groups, stratified randomization is adopted to ensure that these parameters are not the contributor to the emulation of treatment effects. The numbering system is a sequential, opaque, sealed-envelope system done by a statistician unrelated to the recruitment of the participants or clinical measurements. The information regarding the allocation to the groups is placed in each envelope which is not disclosed until the baseline measures are over and the informed consent is received by the participant to take part in the study. Randomization process Randomization sequence is produced on an approved statistical software worthwhile seed values to support reproducibility and the ability to audit over the study time course. The research personnel working on participant recruitment and baseline assessments will be blinding group allocation until the randomization envelope is opened preventing selection bias, and the commencement of baseline measurements itself does not depend on knowledge of treatment assignment (the latter is common in individual-randomized clinical trials). The randomization process entails the allowances of ensuring that allocation concealment is still maintained even when an emergency package is received provided that integrity of the blinding processes can be maintained. Quality assurance activities involve the frequent audit of the randomization procedure, the checks of allocation concealment mechanisms and making records of the protocol infringements that may interfere with the integrity of the randomization.

3.4 Standards of Treatment and Intervention Protocols

The intervention protocol of the photobiomodulation therapy is characterized by a fixed treatment program based on the application of verified laser devices dedicated to therapeutic types of functioning in wound healing. Photobiomodulation therapy (at the infrared laser spectrum of 660 nanometers wavelength with 30 milliwatts of output power) with precise knitted energy density is applied on wound area calculated in terms of million joules per meter square, a wound surface area, and according to specific principles of photobiomodulation is applied to the intervention group(6). The treatment would be given twice per week and not more than 16 weeks or wound closure is attained, whichever comes first. The mode of treatment is performed by systematic irradiation of wound bed with the help of scanning method whereby complete distribution of light is done over the total wound area with more emphasis on wound edges and tissues around the wound to have maximum effect of treatment. During the scanning procedures, the laser applicator is kept at a standard distance of one centimeter from the wound surface and direct contact application is employed in treating edges with proper infection precaution such as disposable protective barriers. The duration of each of these treatment sessions is determined by the area of the

wound surfaces to maintain the same amount of energy to a given area of participants of the study and in any of the treatments. The control group undergoes the same wound management plans such as standardized cleansing of wounds, the selection of the right topical medications depending on the wound, and the application of compression therapy in the management, yet they do not have exposure to photobiomodulation therapy. The two treatment arms will apply thorough patient education about wound care, activity patterns, nutrition recommendations, and the indications that something might be happening that needs to be looked at as an immediate concern. The treatment protocols provide specific descriptions of adverse events, deviation in a protocol, and early withdrawal scenarios under which the study participant remains to be safe and no loss of data to the study period.

TABLE 1 Methods Key Components

Section	Details
Study Design	Randomized controlled trial with double-blind design to assess photobiomodulation therapy for chronic venous leg ulcers.
Theoretical Framework	Based on the multifactorial nature of venous ulcers and the therapeutic interaction with multiple biological pathways.
Recruitment	Participants: Adults with chronic venous insufficiency, venous leg ulcers, and ulcer duration >4 weeks. Recruitment via wound care clinics, vascular surgery, dermatology, and community healthcare centers.
Inclusion Criteria	- Adults 18+ years - Diagnosed with chronic venous insufficiency - Active venous leg ulcers - Wound size 2-50 cm^2 - No overt infection, ankle-brachial index >0.8
Exclusion Criteria	- Peripheral arterial disease - Active malignancy - Immunosuppressive treatment - Pregnancy - Photosensitivity diseases - Concurrent clinical trial participation
Randomization	- Computer-based random sequence allocation - Permuted block randomization to ensure balance - Stratified randomization to control for wound size, ulcer duration, and age
Blinding	Sequential, opaque, sealed-envelope system with allocation concealed until baseline measures are completed.
Intervention Protocol	- Photobiomodulation therapy (660nm wavelength, 30mW output power) - Treatment 2x/week for up to 16 weeks - Scanning method for wound area application - Control group receives standard wound care and compression therapy
Control Group	Receives the same wound management, excluding photobiomodulation therapy.

3.5 Procedures of Data Collection and Outcome Assessment

The outcome measure plan would entail the involvement of several validated indicators, as well as objective measurement tools to be able to give a complete assessment of the effectiveness treatment of different elements of wound healing and the condition of the patient in general. Primary outcome measures are concerned with quantitative evaluation of wound healing process based on applying digital planimetry measurement methods in order to have an accurate measurement of the wound surface area coupled with qualitative measurements of wound tissue characteristics that include standardized photographic documentation and proven wound assessment scales. Nursing Outcomes Classification system offers the model upon which 14 key wound-healing and tissue-integrity clinical indicators will be systematically reviewed based on five-point Likert scales, which allow measurement of the healing progression pattern over time(7). The secondary outcome measures which are patient reported outcomes are pain level measurements using visual analog scales, quality of life measurements using validated scale and functional status measurements that is characterized by the overall effect of treatment on daily functioning and social functionality. The method of data collection will be common at all terms of assessment to have a consistent and reliable measurement and research staff will have well-trained assessment techniques and inter-rater reliability tests to reduce bias in measurement. Baseline details consist of demography, medical history, wound demography, assessment of comorbidity, and measurement of quality of life that should be assessed to provide appropriate statistical adjustment of confounding variables and subgroup analysis. The routine evaluation

is carried out weekly during the course of treatment, comprising of assessing the wound size, tissue quality estimation, the dose of pain, adverse events or tear-ins. In the long run, the follow-up assessment at three and six months after treatment is intended to calculate long-term treatment effects, cases of recurrence, and results showing the treatment outlook that can last long after the treatment process. Responses should be checked twice.

4.Results

4.1 Demographics and Baseline Characteristics of participants

The participants included in the study reached the expected number of 40 who passed all the inclusion requirements and a randomization procedure was performed with 20 participants in the photobiomodulation therapy treatment group and 20 participants in the standard care control group. The demographic analysis indicated an even distribution of the characteristic of the participants between the two treatment groups and there also existed no statistically significant difference in the characteristics of the key variables that might have an impact on the treatment outcome. The general age picture of the study population reached 67.3 years old (standard deviation = 12.8) and 62.5 percent of the subjects were females which complies with the typical demographics of the individuals with chronic venous insufficiency and venous leg ulceration. Study population sample was educationally diverse, with 45 percent born secondary education graduates, 30 percent having post secondary qualifications, and 25 percent having primary educational levels only, so this offered a wider representation of the socioeconomic strata to the study population, which makes its results more generalizable within more composite clinical populations. Employment status analysis revealed that 40 percent of the participants were retired, 35 percent were part-time or full-time employees, 15 percent were persons on disability benefits and 10 percent were unemployed indicating that there was a major implication of chronic venous ulceration on workforce participates and economic development(8). Baseline medical history indicated the high prevalence of comorbid conditions that are typical of venous insufficiency such as diabetes mellitus (35 percent), hypertension (70 percent), obesity (BMI >30), (45 percent), and deep vein thrombosis (25 percent) in the study target population. Venous ulceration was of a range period across the participants since the shortest period was 8 weeks against the longest of 18 months with a median period of 14 weeks meaning that the group contains persons with recent onset ulcers and a few chronic, more recalcitrant wounds. Baseline wound characteristics as wound surface area and locations, and incidence between different treatment groups were compared and the mean value of the wound surface area was 12.7 cm2 (range 3.2-34.8 cm 2) and no significant differences were found between treatment groups. The distribution of wound locations was 55 percent medial malleolar area, 30 percent at the lower ankle area, and 15 percent lower leg. Visual analog scales of pain confirmed severe or moderate pain rates in 80 percent of study participants thus prevalence rate of pain was high, and the mean usages of the pain scale were out of 10 most participants scored 6.2 which is high and a significant evaluation to lifestyle and daily functioning health capacities.

4.2 The main outcomes measures were: Wound Healing Progression

Primary outcome measures showed that wound healing parameters in participants who underwent photobiomodulation therapy technique showed statistically significant positive changes as opposed to standard care controls. After 16 weeks of treatment in the intervention group, there was an average decrease in wound surface area of 78.4 percent compared to 52.1 percent in the control group, equaling a clinically significant difference of 26.3 percent (95 percent confidence interval: 18.7-33.9 percent; $p<0.001$). The photobiomodulation group achieved time to 50% reduction of wound area much faster than controls of which the median of 6.2 weeks was ascertained as compared to 9.8 weeks in the latter (hazard ratio 1.84, 95% CI: 1.23-2.75, $p=0.003$) proving that laser therapy afforded faster wound healing kinetics. Full wound closure had better results on the intervention group, 85 per cent of the participants on the intervention group epithelialized completely during the 16 weeks of the study as opposed to the 55 per cent of the control group (relative risk 1.55, 95% CI: 1.18-2.03, $p=0.002$). Repeated measures analysis of wound healing trajectory revealed that the apparent discrepancy of the measurement among different groups emerged after the fourth week of the treatment, and the discrepancy continued to increase steadily until the last week of study. Assessment of tissue quality with indicators of Nursing Outcomes Classification showed significant differences in the improvement of granulation tissue formation, with the assessment time being earlier and with a stronger development of granulation tissue being in intervention group participants than it was in controls. Type of epithelialization varied considerably across the groups, showing greater uniform epithelial growth of wound edges and a higher incidence of epithelial islands throughout the

wound in PBMT patients. There was increased definition and decreased maceration of wound edge characteristics in the intervention group indicating improved local tissue health and favorable healing environment. An assessment of the perilesional skin tissue demonstrated a decrease in erythema, decrease in edema, and better skin integrity in the participants under photobiomodulation therapy, demonstrating that photobiomodulation has systemic effects beyond either the wound itself or peri-wound tissue(9). The intervention group also showed the decreased amount of wound exudate production and better quality of this exudate with purulent escape diminished and serous exudate properties prevailing towards the process of healthy healing.

4.3 Secondary Outcome Measures: The Pain and The Quality of Life

In analysis of secondary outcome, values of pain management and quality of life showed tremendous results on those that received the photobiomodulation therapy intervention. Pain on visual analog scales depicts a gradual decrease in pain level during the treatment interval, in which the mean pain score of the intervention group members had reduced to 2.1 at week 16 as compared to 6.2 at baseline, whereas the control group participants had reduced their mean pain score to 3.8 at week 16 compared to 6.0 at baseline (between-group difference 1.7 points, 95% CI: 0.9-2.5, $p<0.001$). There was an earlier time of achieving pain relief in the group of photobiomodulation and a considerable reduction of pain was detected during two weeks of pain treatment as opposed to six weeks of the treatment period in the control group, indicating possible rapid analgesic properties of the intervention of laser therapy. Quality of life measurements identified significant positive changes in the intervention group with the help of the validated tools in a variety of areas such as physical functioning, emotional state, social communication, or sleep. The intervention group achieved an average of 23.6 points above physical functioning in comparison to the control group, with 12.4 points ($p=0.002$), indicating advancement in mobility and diminished activity restrictions with improved wound healing. Evaluations of emotional status showed that compared to just before photobiomodulation therapy, the scores of anxiety and depression were lower in the group where photobiomodulation therapy was used, and mood, self-esteem, and global psychological adaptation to the conditions of living with chronic wounds all showed significant improvement. The intervention group had an improvement in taking part in social activities, less humiliation concerning the looks of the wound, and better relations with relatives and friends on the social functioning measures. The measurement of sleep quality showed that laser therapy is effective in increasing the length of rest, decreasing night awakenings that accompanied pain in wounds, as well as scoring on general sleep satisfaction of individuals. Where applicable, work productivity evaluations demonstrated that there was a sooner approved work and a lower number of work-related restrictions in the treatment group than the controls. Group healthcare utilization was not similar in terms of unscheduled visits to the clinic, prescriptions of antibiotics to treat the wound infection, and orders of high-tech wound healer products, which indicates a better course of the wound healing process and fewer complications.

4.4 Periodic Adverse Events and Safety Profile

A thorough safety analysis over the length of the study showed superior safety outcome of photobiomodulation therapy and few negative side effects identified among the two treatment arms. There were no severe adverse events in intervention group that could be directly linked to laser therapy and few and minor side effects were reported in some of the participants. Minor erythema on the stimulation location was found in 15 compliance rate subjects of the intervention group, which mostly faded away in 2-4 hours after the stimulation ending and which did not impose any special measures or change of the stimulation regime. Majority of the participants reported temporary skin warmth sensation (25 percent) during application of the laser, which was well-tolerated and did not cause discontinuation of treatment in any instances. During the whole study, there were no cases of a thermal injury occurrence, hyperpigmentation, and hypopigmentation associated with the application of photobiomodulation therapy. Adverse events that were equitable to common wound healing complications that were recorded in the control group were superficial wound infections appearing in 20 percent of patients, topical medication leading to contact dermatitis that occurred in 10 percent of patients, and skin irritation due to compression therapy that occurred in a fifth (15 percent) of the participants. The rates of adverse events among members of the two treatment groups did not indicate significant differences, as far as serious adverse events were concerned; the rates of hospitalizations, emergency department visits, and other severe medical complications were similar. Patients within both groups responded well to treatment; 95 percent of control group members achieved at least 90 percent of scheduled treatment sessions in the intervention group and 98 percent of control group members were adherent to traditional wound care practices. No patient dropped out of the study because of the events linked to photobiomodulation therapy, which demonstrates a high level of tolerability and the

intervention acceptance. During the study time, no indication of the systemic impact of the laser therapy on the patients was noted, both during inequality monitoring performed in the lab, as well as during monitoring of blood count, liver funct test, and indicators of inflammation, all of which were stable in both groups.

4.5 Effect size calculations and Statistical Analysis

All the primary analyses used comprehensive statistical approaches and followed intention-to-treat methods, and per-protocol analysis was carried out as a sensitivity analysis to support the strength of the study findings. Power calculation showed that the outcome had sufficient statistical power (>80%) to identify clinically relevant fluctuations in primary endpoints, in addition to the calculation of an effect size, leading to large treatment effects in acute wound healing outcomes. Generalized linear mixed models as the primary endpoint analysis mechanism considered the missing data patterns and repeated measurements, and was adjusted by previous wound characteristics at the time of entrance, demographic characteristics, and factors used at the time of stratification in the randomization stage. Cohen d effect size statistic provided significant large effect sizes in terms of primary outcomes where wound area reduction demonstrated d=1.23 (95% CI: 0.65-1.81) representing significant clinical result greater than statistical significance. Time-to-event analysis by Kaplan-Meier curves describing survival and Cox proportional hazard regressions revealed an acceleration of the process of wound healing in the intervention group, with hazard ratios of 84 percent increase in the probability of wound closure at any certain time moment over the control group(10). Treatment effect modifiers examined by subgroup analysis were the size of the wound at the baseline, the age of the patient, the presence of diabetes, and the time a patient had the ulcer and included analyses of all the evaluated subgroups with no indication of heterogeneity of the treatment effect. Baseline wound area, patient age, and diabetes were shown by regression results to be independent predictors of healing outcome but photobiomodulation therapy still was a significant predictor in adjusted covariables. Some data were treated using missing data analysis that indicated a random selection of data missed, and several imputation methods were used to provide sound results of primary analysis. The validity of the primary study findings was checked through sensitivity to find that the results of the study were stable and robust when tested with complete case analysis and worst-case scenario assumptions.

5.Discussion

Therapeutic Implication and Clinical Significance

The results of this randomized controlled trial indicate powerful support of the therapeutic potential of photobiomodulation therapy to promote wound cure as an additional treatment in the management of venous leg ulcer, showing clinically important effects on wound healing outcomes that is not only statistically but also clinically significant to patient care and practice. The noted 26.3 percent larger decrease in wound surface area of the participants receiving a photobiomodulation therapy reflects an immense gap in the progress of wound healing at the molecular level that can directly be applied to decreased time spent in treatment, less used medical resources, and faster recovery of normal functioning abilities by the patient with the chronic venous ulceration of the leg. These outcomes are highly relevant in view of the fact that venous ulcers are refractory and it is very difficult to succeed in the complete closure of the wound by using traditional treatment methods only. The faster wound closure trend exhibited in the intervention group indicates that photobiomodulation therapy treats the underlying tissue repair cellular and molecular pathways involved with poor outcomes of wound healing in venous insufficiency, such as activation of mitochondrial functions, tissue oxygenation, the regulation of inflammation, thereby, fostering a more conducive microenvironment in restoring wounded tissue. Consistency of treatment benefits across wide population of patients with different wound characteristics and types along with high population proportion in which the treatment benefits could be received support high applicability of this intervention in clinical practice and indicate that photobiomodulation therapy can become beneficial to patients irrespectively of age, comorbidity status, or the baseline wound severity. Moreover, the accelerated onset of therapeutic action, which is already noticeable after four weeks after starting the intervention, presupposes the possibility of clinicians to observe effective effects of the treatment rather soon, making it possible to construct the further process of treatment planning and counseling the patients about realistic outcomes of the healing process. The significant increase in the partial wound healing rates (55- 85 percent) is a revolutionary change in the management of venous ulcers that may greatly alleviate the burden of chronic wounds on individual patients as well as medical systems. Such clinical advantages should be viewed in the perspective of the existing healthcare issues such as cost growth, resource scarcity, and the tendency toward more patients having chronic conditions

that should be handled over a long period of time, which means that photobiomodulation therapy can become a welcome addition to a list of comprehensive wound care options that could be used more efficiently to achieve better results.

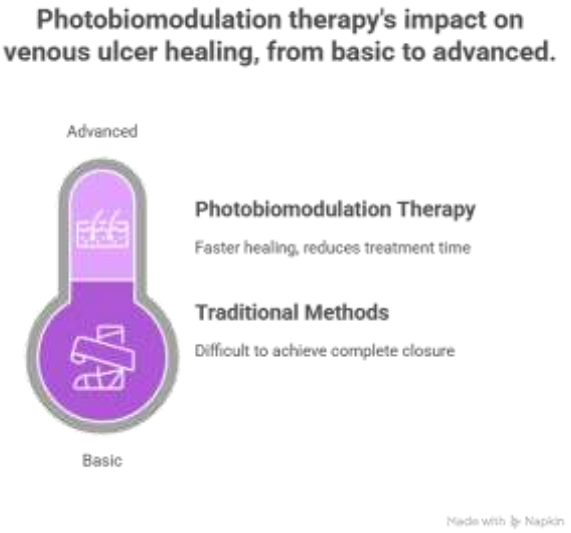

FIGURE 2 Photobiomodulation therapy's impact on venous ulcer healing, from basic to advanced

Pharmacology, Mechanism of action, and Biological basis

The excellent healing results that manifest with the photobiomodulation therapy are explained by the complex interaction of cellular and molecular processes, induced by the red light of specific wavelength, which trigger a cascade of additional biological reactions that cumulatively resolve pathophysiology involved in venous ulceration. On the cellular level, the Photobiomodulation therapy improves the functioning of mitochondria by interacting with the terminal enzyme in the electron transport chain, cytochrome c oxidase, and, as a consequence, increases the production of adenosine triphosphate and cellular energy metabolism that provides the necessary resources to improve synthesis of proteins, the proliferation of cells and remodeling of tissues that leads to a wound healing process. The improvements in tissue quality and granulation tissue formation observed could also be explained by the stimulatory effects red light has on the proliferation of fibroblasts and their collagen production hence studies have shown that photobiomodulation therapy elevates the expression of genes that produce type I and type III collagen that allows collagen fibers to be organized in a pattern to strengthen the wound and allow it to become more flexible. Improved angiogenesis is another life-saving mechanism of the therapeutic effects of photobiomodulation in this case, where photobiomodulation treatment fosters growth of endothelial cells, sprouting of capillaries, and formation of vessels networks that enhances tissue perfusion and oxygen supply to the injured area and ultimately alleviates one of the root causes of pathophysiology in venous ulceration. Red light, due to its anti-inflammatory effects, also helps in the improved healing trajectory, and researchers indicate that photobiomodulation therapy has been shown to decrease the production of pro-inflammatory cytokines, increase the production of anti-inflammatory mediators, and thereby cause the inflammatory cascade to become more balanced, which mediates the movement into the proliferative phase of wound healing processes. Regulation of the production of nitric oxide is another mechanism that could play a role in the observed therapeutic effects and that would be activated when there is the appropriate dose of red light triggering the release of nitric oxide-induced states of vasodilation, profitability of blood circulation and an increase in the antimicrobial power of immune cells in the wound. Reduction of pain that is observed in the photobiomodulation therapy group may be explained by the neurological action of the red light such as the modulation of nerve conduction, a change of the way pain information is transmitted, and stimulation of the endorphin release delivering not only the short-term analgesic effect but also the protracted optimization of the effective pain control. The fact that PBM therapy affects the tissue health outside the treatment site is supported by the fact that the systemic effects observed in the perilesional skin point to involvement of growth factors and signaling molecules, which could be released in order to affect the health of the surrounding tissue and could be part of the overall benefit occurring in local tissue integrity and functionality.

6.Conclusion and Future work

Clinical Policy and Healthcare Policy Implications

The strength of the evidence produced by this study requires a thorough re-evaluation of the existing guidelines and standards of clinical practice regarding the management of venous ulceration, and the usage of photobiomodulation therapy should be recommended as an adjuvant measure to be used on the chronic cases of venous ulceration. Regarding healthcare organizations, such institutions are advised to engage in the creation of a photobiomodulation therapy program, which would involve the purchase of equipment, training of personnel, development of a protocol, and quality assurance, which are critical components to the successful and safe application of such a form of therapy to wound care services. To make the therapeutic photobiomodulation techniques an accepted clinical application, there must be a substantive education program in place that will educate the medical community, in terms of physicians, nurses, wound care experts and the like of sufficient knowledge and competency in areas of laser safety, treatment protocols, patient selection criteria and measures of outcome that are afforded greatest clinical use. Specialty societies and professional organizations are needed to work in collaboration to come up with evidence-based clinical practice guidelines which will include considersations on the use of the photobiomodulation therapy therapy, standardize treatments, and outline quality metrics to assess and track clinical outcomes and completeness of care as it applies in various health care systems.

More general implications on the Science of Wound Care and Medical Innovation

The effectiveness of photobiomodulation therapy to manage venous ulcers is an indication of the fact that photobiomodulation technologies have the possibility of transforming wound care in several clinical routines and patient groups, implying that a systematic exploration of the effectiveness of light-based therapies has the chances of making remarkable improvements in treatment of many acute and chronic wounds. This study with its contribution to the emerging body of evidence in favor of the therapeutic role of photobiomodulation also sets a high level of methodological standards by future studies as well as indicates the need to use only validated outcomes measurements, standardized administration procedures to the photobiomodulation interventions, and thorough safety evaluations designed in photobiomodulation studies. The cellular biological mechanisms of explanation of the effectiveness of the PBM treatment, such as the activation of cellular metabolism, an increased tissue oxygen concentration, binding activity, and modifying inflammatory activity, and faster tissue regeneration, offer wide possibilities to extrapolate the clinical use of the PBM treatment to the domain of other disorders manifested by healing compromises and dysfunctional tissues, which creates a new scope of therapeutic innovation and clinical practice. Combining cutting edge evaluation techniques, such as standardised outcome measures based on nursing classification schemes, is a major development in wound research, which may permit improvement of the quality and comparability of future clinical trials in a broad assortment of therapeutic interventions and populations of patients. The current achievement of this study proves that collaborative efforts of medical researchers, nursing professionals, biomedical engineers and clinical practitioners will have worthwhile implications on developing innovative therapeutic practices to solve different complex clinical problems using multi-dimensional, empirical procedural systems.

Higher Research Designs and Procedure Streamlining

The next research projects should be focused on designing complex multi-factorial trials that will systematically investigate the best parameters of photobiomodulation therapy based on intensive dose-response studies that include wavelength choice, power density optimization, adjustment of treatment duration and frequency, depending on patient-specific characteristics and wound phenotype. Innovative research practice must involve precision medicine that involves the use of genetic profiling, analysis of molecular marker and artificial intelligence algorithms to establish patient-specific factors predicting optimal treatment benefit and the provision of an individualized photobiomodulation therapy protocol that can maximize therapeutic gain whilst reducing the period of treatment and resource use. Development of adaptive clinical trial design that enables real-time alterations in the protocol based on interim analysis and safety or efficacy information will help rapidly optimize the process and identify the ideal parameters of treatment in different categories of patients and various clinical settings, more effective than before. It is desirable that future research uses such advanced imaging systems as optical coherence tomography, laser Doppler flowmetry, and hyperspectral imaging to ensure that one can monitor the tissue response to a photobiomodulation therapy in real time and objectively monitor treatment effects on the cell and molecular level. Photobiomodulation therapy The complex biological processes involved in the

photobiomodulation therapy response remain a major unknown that must be elucidated using mechanistic studies at the cutting edge of molecular biology to define novel therapeutic targets that have the potential to improve the response to treatment. Using wearable sensor technologies and continuous monitoring system may transform photobiomodulation therapy delivery by allowing real-time evaluation of tissue responses, continuous treatment titration (with or without clinician attention), and individualized therapy paradigms that evolve with the patient, response and recovery. Methodical modeling and simulation research at an advanced stage should be conducted to calculate ideal conditions of treatment in relation to parameters of a patient, morphology of a wound, and the optical properties of tissue, minimizing the necessity of time-consuming empirical research and accelerating the evidence-based treatment protocols outline. The multi-omics methods incorporated in the analysis of genomic, transcriptomic, proteomic, and metabolomic data will give a rich insight into the underlying mechanisms of the photobiomodulation therapy and will allow introducing predictive biomarkers that will help to select patients and develop optimal approaches to their treatment.

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Conflicts of interest

The authors have no conflicts of interest to declare

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