












## Research Article

# A Novel, Hand-Held, and Low-Level Light Therapy Device for the Treatment of Acne Vulgaris: A Single-Arm, Prospective Clinical Study

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There is an increasing demand for low-level light therapy devices for the treatment of dermatologic conditions, such as acne, hair loss, undesirable body hair, and skin aging. This study evaluated the safety and effectiveness of a novel hand-held low-level light therapy device with a 680 nm red laser diode and a 450 nm blue light-emitting diode for the treatment of mild-to-moderate acne. A prospective clinical study was conducted on 57 patients with mild-to-moderate acne and Fitzpatrick skin types II–IV. Treatments were self-administered by the patients at home daily for 4 weeks. Conventional treatment was restricted during the study period. The number of inflammatory and noninflammatory lesion counts, Investigator's Global Assessment grade, patients' self-assessment, and adverse events were measured every two weeks, and follow-ups were performed until four weeks after the final treatment. Moreover, we evaluated the bactericidal effect of low-level light therapy on *Cutibacterium acnes*, a causative agent of acne vulgaris, in vitro. The mean number of inflammatory acne lesions decreased statistically at weeks 4 (\*\* $p < 0.001$ ) and 8 (\*\* $p < 0.001$ ). The proportion of Investigator's Global Assessment grade 3, indicating moderate acne severity, decreased significantly at the final visit. No severe adverse reactions were reported. Furthermore, there was a significant reduction in the viability of *Cutibacterium acnes* following low-level light therapy exposure in vitro. The results of this study demonstrate that this novel, hand-held, and low-level light therapy device are safe and effective for the treatment of inflammatory acne, with good adherence.

## 1. Introduction

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous units, affecting approximately 85% of adolescents and young adults [1]. Although acne vulgaris is not life-threatening, it can significantly affect the patients' self-

esteem and quality of life. Previous studies have found the impact of acne on the social, emotional, and vocational aspects of quality of life [2–4]. Excess sebum production, abnormal keratinization, colonization by *Cutibacterium acnes*, and skin inflammation are the four major pathogenic factors involved in acne vulgaris. Although topical antibi-

otics and retinoids are the standard antiacne medications for mild to moderate acne, a variety of side effects, including irritation, antibiotic resistance, and the teratogenicity of isotretinoin, have been challenging [5, 6]. Therefore, there is a substantial unmet need for alternative acne treatment options.

With the growing medical demand for light-based therapies, several different types of lasers have been used extensively in the treatment of patients with acne [7–9]. However, with these laser treatments, it may take at least a few days or weeks for the skin to fully recover. Low-level light therapy or photobiomodulation refers to the use of photons at nonthermal irradiance to alter biological activity, and has been shown to reduce pain and inflammation, promote tissue regeneration, and prevent tissue damage [10]. Recently, the efficacy of low-level light therapy has been widely established in dermatology and has shown good efficacy in the treatment of acne vulgaris [11–13]. There have been several reports on the clinical improvement of acne lesions with blue light treatment, suggesting that low-fluence blue light irradiation induces photoexcitation of protoporphyrin IX and coproporphyrin III, which leads to the destruction of *Cutibacterium acnes* [14–16]. In contrast, red light penetrates deeper and has better anti-inflammatory effects, activating the release of multiple transcription factors and cytokines in various cell types. According to some studies, red light has been reported to increase nitric oxide release and reduce TNF- $\alpha$  and COX-2 expression [17–19]. In addition to the efficacy of each individual wavelength, numerous attempts have demonstrated that the combination of blue and red light is synergistic in treating acne lesions by integrating antibacterial and anti-inflammatory effects [20–22]. Papageorgiou et al. compared the efficacy of blue light against mixed blue and red light in the treatment of acne, and the effect of mixed light was evaluated to be better [20]. Nonetheless, clinical studies evaluating the effectiveness of blue-red combined phototherapy in the treatment of acne are lacking. There is currently no consensus on a treatment regimen for acne vulgaris with low-level light therapy.

The COVID-19 pandemic has increased the demand for noncontact medical procedures among healthcare providers and patients, and advancements in solid-state light sources have enabled the commercialization of at-home light therapy devices [23, 24]. Employing a practical and user-friendly home-based light device significantly enhances adherence and compliance among acne patients, owing to its satisfactory efficacy and favorable safety profile [25]. Therefore, in this study, we aimed to evaluate the clinical effectiveness of a hand-held blue-red combined low-level light therapy device for patients with mild to moderate acne using a self-treatment method. In addition, to provide a better understanding of the effect of blue-red combined phototherapy on antibacterial properties and in vivo skin extracellular matrix remodeling, we assessed its antibacterial potential against *Cutibacterium acnes* and evaluated the role of low-level light therapy in skin extracellular matrix remodeling in SKH1 mice.

## 2. Materials and Methods

### 2.1. In Vitro and in Vivo Experiments

**2.1.1. The Blue-Red Combined Photomodulation Device for Potential Low-Level Light Therapy.** The light source used in this study was a commercially available device, P1-FOX (PAD-FA120, Ptech Corp., Pyeongtaek, Gyeonggi-do, Korea), which is composed of three blue lights (wavelength = 450 nm) of light-emitting diodes and six red lights (wavelength = 680 nm) of laser diodes. The light-emitting diode emits a power of 11.7 mW/cm<sup>2</sup> and the laser diode emits a power of 13.3 mW/cm<sup>2</sup>. This product functions via 625-Hz pulse operation and performs the cross-output of three light-emitting diodes and six laser diodes every four seconds (Supplementary Figure 1).

**2.1.2. *Cutibacterium acnes* Culture and Investigation of the Antibacterial Properties of the Blue-Red Combined Photomodulation Device.** To investigate the antibacterial properties of blue-red combined photomodulation, we serially diluted *Cutibacterium acnes* and cultured them on Brucella agar plates after 20 min of exposure to the blue-red combined photomodulation (Figure 1(a)). *Cutibacterium acnes* was used to assess the antibacterial properties of the blue-red combined photomodulation device. *Cutibacterium acnes* (KCTC 5933) were purchased from the Korean Collection for Type Cultures (Daejeon, Korea). *Cutibacterium acnes* was grown for 48 to 72 h at 37°C on Brucella agar plates (BANDIO, Pocheon, Gyeonggi-do, Korea) under anaerobic conditions using Oxoid™ AnaeroGen™ 2.5 L Sachet (Thermo Scientific, Waltham, MA, USA) in anaerobic jars (Sigma-Aldrich, St. Louis, MO, USA). Single colonies from the plate were picked and inoculated into 5 mL of brain heart infusion broth (Kisan Bio, Seoul, Korea) in a round-bottom tube. The bacterial suspension was incubated at 37°C in a shaking incubator at 160 rpm until visible growth was observed. Bacteria were diluted to an OD600 value of 0.1. Diluted bacterial suspensions were divided and tested under two conditions: no low-level light therapy (control group) and low-level light therapy treatment (experimental group). Aliquots of 500  $\mu$ L of the diluted bacterial suspensions were placed into the wells of a 24-well plate, and blue light was placed directly on top of the 24-well plate, approximately 5 mm from the surface of the liquid. The plates were then incubated in the dark at 37°C. After low-level light therapy exposure, the bacterial suspensions were serially diluted 10-fold in brain heart infusion broth. Next, 3  $\mu$ L of each well was spotted onto Brucella agar plates (BANDIO, Pocheon, Gyeonggi-do, Korea) to quantify the survival after low-level light therapy exposure [26]. After 24 h of incubation under anaerobic conditions, the plates were examined and scored for growth.

**2.1.3. RNA Isolation and Quantitative Polymerase Chain Reaction.** RNA was isolated from the mouse skin using the TRIzol reagent (Invitrogen, Carlsbad, USA). RNA was quantified using a spectrophotometer (Thermo Scientific™,

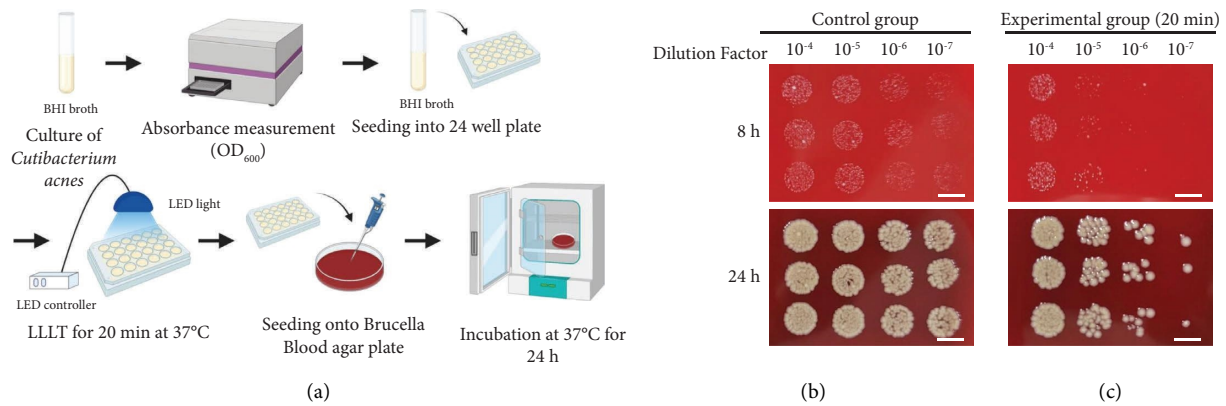


FIGURE 1: Assessment of the antibacterial properties of low-level light therapy against *Cutibacterium acnes*. (a) A schematic illustration of antibacterial evaluation (created with <https://BioRender.com> accessed on November 21, 2022). (b) Gross images of Brucella agar plates. (c) Representative photographs showing colonies of *Cutibacterium acnes* irradiated with blue light-emitting diode for 20 min and cultured for 8 h and 24 h in blood agar plates (scale bar = 5 mm).

Waltham, MA, USA). The isolated RNA was reverse-transcribed into cDNA using ReverTra Ace™ qPCR RT Master Mix with gDNA remover (Toyobo, Osaka, Japan) and a thermal cycler (T100™ Thermal Cycler, Bio-Rad, Hercules, CA, USA). Quantitative polymerase chain reaction was performed using the SYBR Green Real-Time PCR Master Mix Kit (Toyobo, Osaka, Japan) on a StepOnePlus Real-Time PCR system (Applied Biosystems, Foster City, CA, USA) at the Soonchunhyang Biomedical Research Core Facility of the Korea Basic Science Institute. All samples were run in triplicate, and relative quantification of gene expression was performed using the  $2^{-\Delta\Delta C_t}$  method, as previously reported [27]. Gene expression levels were normalized to 18 s as a reference gene. Primer sequences used in this study are listed in Supplementary Table 1.

**2.1.4. Investigation of in Vivo Toxicity of the Blue-Red Combined Low-Level Light Therapy Using SKH1 Mice.** Male SKH1 mice were purchased from Orient Bio (Seoul, Republic of Korea). All animal experimental procedures were approved by the Institutional Animal Care and Use Committee of Soonchunhyang University (Animal protocol number: SCH22-0012). To perform low-level light therapy, four 8-week-old SKH1 male mice were anesthetized with 1% isoflurane inhalation prior to the treatment. The low-level light therapy device was placed directly on the surface of the mouse skin, approximately 5 mm away from the surface of the skin, and the mice were exposed to the blue-red combined photomodulation for 20 min. After 6 h, the mice were sacrificed for analysis.

**2.1.5. Histological Evaluation.** The dorsal skin of each mouse was collected at the end of the experiment. The tissue was fixed with 4% paraformaldehyde in phosphate-buffered saline for 24 h, dehydrated gradually in ethanol, and embedded in paraffin. The paraffin-embedded samples were sectioned into 5  $\mu$ m-thick sections to be processed for hematoxylin and eosin and Masson's trichrome staining for histological evaluation, as previously described [28]. Briefly,

paraffin-embedded samples were deparaffinized with CitriSolv and rehydrated in phosphate-buffered saline before staining. For hematoxylin and eosin staining, sections were stained with hematoxylin (Mayer's modified; Abcam, Cambridge, UK) and eosin (Sigma-Aldrich, St. Louis, MO, USA). For Masson's trichrome staining, the tissue sections were stained with iron hematoxylin and Biebrich scarlet-acid fuchsin solution (Polyscience, Niles, IL, USA), according to the manufacturer's instructions. All bright-field images were acquired using an inverted microscope (Eclipse Ti-U, Nikon, Tokyo, Japan) at the Soonchunhyang Biomedical Research Core Facility of the Korea Basic Science Institute.

## 2.2. Clinical Trials

**2.2.1. Study Design and Patient Enrollment.** This study employed a single-arm prospective design, and all patients were treated in the clinic of the Department of Dermatology at Soonchunhyang University Hospital, Cheonan. This study was conducted from April 2019 to December 2019, in accordance with the ethical guidelines of the World Medical Association Declaration of Helsinki, and was approved by the Institutional Review Board (IRB) of Soonchunhyang University Cheonan Hospital (IRB number: 2018-06-028). All patients provided written informed consent prior to enrollment. Eligible participants older than 15 years with mild-to-moderate facial acne (Investigator's Global Assessment grade II-III) were included. None of the subjects had received laser- or light-based therapy for at least 6 weeks before enrollment, dermabrasion, trichloroacetic acid peel, botulinum toxin type A, dermal fillers, photodynamic therapy, cosmetic surgery, or oral retinoid treatment within the past 6 months, and had not received oral antibiotics or oral contraceptives within the past 3 months. Patients were also excluded if they used topical alpha hydroxy acids, retinoic acid, retinol, salicylic acid, vitamins C and D, or their derivatives within 6 weeks prior to enrollment. Finally, pregnant and breastfeeding patients were excluded from the study. The baseline characteristics of the 57 patients with mild-to-moderate facial acne enrolled in the study are shown in Table 1.

TABLE 1: Baseline characteristics of the patients.

Variables	Total
Sex	
Male	38
Female	19
Age (years)	21.67 ± 3.90
Disease duration (months)	9.53 ± 2.43
Skin phototype (Fitzpatrick)	
II	10
III	33
IV	14
Inflammatory lesion counts	9.54 ± 5.26
Noninflammatory lesion counts	7.54 ± 3.85
Investigator's Global Severity Assessment grade	2.51 ± 0.50
Grade 4 (severe)	0
Grade 3 (moderate)	29
Grade 2 (mild)	28
Grade 1 (almost clear)	0
Grade 0 (clear)	0

**2.2.2. Devices and Treatment Protocols.** All enrolled patients were given a hand-held blue-red combined low-level light therapy device. All patients had mild-to-moderate facial acne and were instructed to turn on the device after adjusting the panel to align the facial acne lesions as closely as possible. The treatment was performed twice a day for 10 min for each treatment for 4 weeks, regardless of the severity of the acne. The device has a self-recording program to assess patient compliance and actual usage time. Post-treatment follow-up assessments were conducted two and four weeks later. All patients were encouraged to use a nonirritating cleanser (Zeroid foam cleanser, Neopharm, Daejeon, Korea) and moisturizer (Zeroid soothing cream, Neopharm, Daejeon, Korea), as well as a noncomedogenic sunscreen on their face.

**2.2.3. Evaluation of Blue-Red Combined Low-Level Light Therapy on Skin Regeneration.** Efficacy analysis was performed in the intention-to-treat and per-protocol populations. The intention-to-treat population included patients who received at least one treatment and had at least one on-study visit upon inclusion in the study. The per-protocol population included all patients who received at least 80% treatment. The subjects were carefully assessed at 2-week intervals at baseline (weeks 0, 2, and 4) and followed-up until 4 weeks after the final treatment (weeks 6 and 8). Standardized digital photographs capturing the frontal and bilateral 45° sides for assessment of full facial acne lesions were taken during each visit, using identical positions and camera settings (Janus Premier, PIE Co., Suwon, Korea) to ensure the reliability of the evaluation. Efficacy evaluation was performed using the number of acne lesions on the entire face from the hairline to the jawline. The acne lesions included in the count were comedones, papules, pustules, and nodules. A global severity assessment, according to the Investigator's Global Assessment, was also conducted (Supplementary Table 2). The Investigator's Global Assessment grade was recorded in a blinded manner by three

independent dermatologists (CEH, LSH, and KJE). In addition, patients recorded their self-assessments of the therapeutic effectiveness during each visit using a visual analog scale; at baseline, a disease-free state was designated as 0, and a state of severe acne was designated as 10. All adverse effects including pruritus, pain, erythema, scaling, and hyperpigmentation were recorded in detail throughout the study.

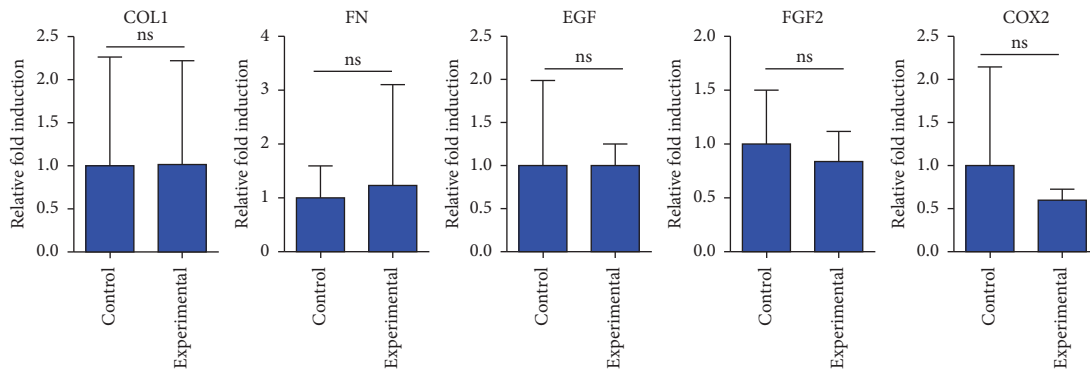
**2.3. Statistical Analysis.** Demographic characteristics are expressed as means ± standard deviation for continuous variables and as frequencies and percentages for categorical variables. Treatment effects were compared with the baseline scores at each follow-up visit using paired *t*-tests. The statistical analysis was performed using both the intention-to-treat (ITT) and the per-protocol (PP) analysis sets. The ITT analysis set included all randomized participants, while the PP analysis set was restricted to participants who remained adherent to the study protocol. We applied the last-observation-carried-forward (LOCF) rule for missing data. Data were analyzed using SPSS Statistics (version 26.0, IBM Corp., Armonk, NY, USA). In all analyses, \*\*\**p* < 0.001 was considered to indicate statistical significance.

### 3. Results

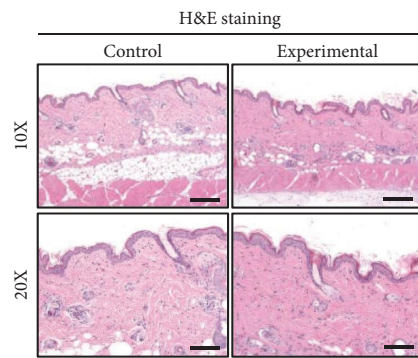
**3.1. Effect of Blue-Red Combined Photomodulation on *Cutibacterium acnes* Growth.** As shown in Figures 1(b) and 1(c), we observed a significant decrease in the number of *Cutibacterium acnes* colonies upon blue-red combined photomodulation as a function of the initial bacterial concentration. These results demonstrated the antibacterial properties of blue-red combined photomodulation, exhibiting the inhibition of *Cutibacterium acnes* growth.

**3.1.1. Investigation of *in Vivo* Toxicity of Blue-Red Combined Photomodulation Exposure Using an Animal Model.** To confirm the effect of blue-red combined photomodulation, we assessed the mRNA expression and histological changes in SKH1 mouse skin upon blue-red combined photomodulation to precisely evaluate whether 20 min of blue-red combined photomodulation would induce skin damage in both the epidermal and dermal layers of SKH1 mouse skin tissues. As shown in Figure 2(a), genes associated with skin extracellular matrix remodeling, such as *Col1α1*, fibronectin, EGF, and FGF2, did not show any significant changes. Additionally, although COX2, which is an inflammation marker, was slightly decreased in skin tissues with blue-red combined photomodulation, it did not show a significant difference (*p* > 0.05).

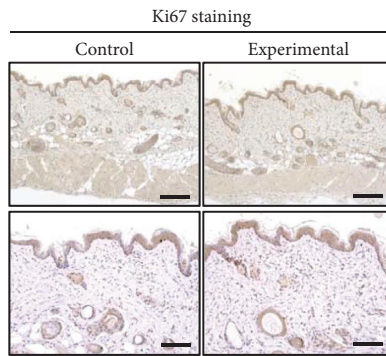
To further evaluate whether blue-red combined photomodulation could cause damage to the skin tissues and cytotoxic effects on the cells present within the epidermis and dermis, we performed a histological evaluation. As shown in Figures 2(b)–2(d), hematoxylin and eosin and Masson's trichrome staining demonstrated that there was no damage to either the epidermis or dermis, and collagen deposition in the dermis seemed to be intact in both the



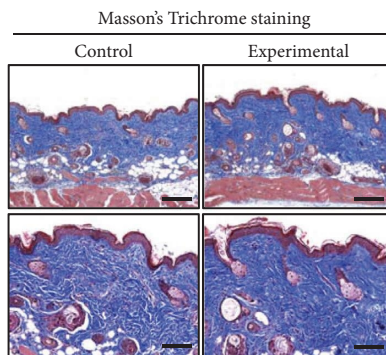
(a)



(b)



(c)



(d)

FIGURE 2: (a) Quantitative polymerase chain reaction analysis of skin extracellular matrix remodeling-/inflammation-related genes. The levels of gene expression of the experimental groups (low-level light therapy treatment for 20 m) were normalized to the levels of the control group (no low-level light therapy); 18 s was used as the reference gene. Values are presented as means  $\pm$  standard deviation. “ns” indicates that there is no statistical difference. Histological evaluation of skin tissues from SKH1 mice with or without 20 m low-level light therapy treatment. (b) Hematoxylin and eosin staining of SKH1 skin tissues for skin extracellular matrix (pink) and nuclei (purple). (c) Ki67 staining for visualizing proliferating cells’ nuclei (dark brown) within SKH1 skin tissues. (d) Masson’s trichrome staining of SKH1 skin tissues for collagen (blue) and cytoplasm (pink). (Magnification, 10x: scale bar = 200  $\mu$ m, Magnification, 20x: scale bar = 100  $\mu$ m).

control and experimental groups. Moreover, Ki67 immunohistochemistry revealed no significant differences in the numbers of Ki67 positive nuclei, indicating that blue-red combined photomodulation did not cause apoptosis of cells in both the epidermis and dermis layers. Taken together, these results suggest that blue-red combined photomodulation does not have a detrimental effect on skin homeostasis and extracellular matrix remodeling.

**3.2. Clinical Trials.** The intention-to-treat population consisted of 57 patients, whereas the per-protocol population consisted of 46 patients. Among the 11 patients who were excluded from the per-protocol population, 6 patients failed to comply with the treatment protocol due to nonadherence according to the self-recording program of the device, and the remaining 5 patients were withdrawn from the study due to their inability to visit the hospital. Efficacy variables were analyzed in the intention-to-treat and per-protocol populations.

**3.2.1. Evaluation of Treatment Efficacy in the per-Protocol Population.** After two weeks of low-level light therapy treatment, inflammatory acne counts were significantly reduced (40.6% reduction, from a score of 9.59 to 5.70,  $p < 0.001$ ). The number of inflammatory lesions decreased gradually during the four weeks of treatment (45.4% reduction, from a score of 9.59 to 5.24,  $p < 0.001$ ). Eventually, at the final visit (week 8, 4 weeks after the final treatment), the final counts decreased by 64.7% (from a score of 9.59 to 3.39,  $p < 0.001$ ). A statistically significant reduction was evident in the mean inflammatory lesion count as early as week 2, and the improvement was maintained at the end of treatment ( $p < 0.001$ ; Figure 3(a)). There were no differences in the number of noninflammatory lesions (Figure 3(b)). Clinical pictures of the two patients with marked improvement are shown in Figures 3(c) and 3(d). Aligned with the results of the inflammatory acne lesion counts, the proportion of the Investigator's Global Assessment grade 3 indicating moderate acne severity decreased significantly from 52.2% at the baseline to 15.2% at week 2 and to 0% at final visit (Figure 3(e)). Before treatment, patients' self-assessment of their acne was given a visual analog scale score of 10. Throughout the course of treatment, the visual analog scale score decreased significantly from 8.24 at baseline to 3.52 at the final visit (Figure 3(f)).

**3.2.2. Evaluation of Treatment Efficacy in the Intention-to-Treat Population.** Inflammatory acne counts were significantly reduced by low-level light therapy (38.8% reduction, from a score of 9.54 to 5.84,  $p < 0.001$ ) after 2 weeks of treatment. During the four weeks of treatment, the counts decreased gradually (42.2% reduction, from a score of 9.54 to 5.51,  $p < 0.001$ ). Moreover, at the final visit (week 8, 4 weeks after the final treatment), the counts decreased by 59.3% (from a score of 9.54 to 3.88,  $p < 0.001$ ). A statistically significant reduction was evident in the mean inflammatory lesion count as early as week 2, and the improvement was

maintained at the end of treatment ( $p < 0.001$ ; Figure 4(a)). There were no differences in the number of non-inflammatory lesions (Figure 4(b)).

**3.2.3. Safety and Patient Compliance.** To assess patient adherence to treatment, we analyzed the usage data recorded on the devices. Four patients did not complete the daily use program, whereas the other patients regularly used the devices throughout the study. Among these 57 patients, neither severe adverse reactions nor adverse effects (e.g., skin dryness, erythema, or desquamation) were reported.

## 4. Discussion

The versatility of low-level light therapy has been proven by its application in various conditions that require stimulation of healing, pain relief, and inflammation [29, 30]. Low-level light therapy has positive effects on wrinkles, acne scars, hypertrophic scars, and burn healing. In addition, it might benefit inflammatory diseases such as acne. The noninvasive nature and absence of side effects promotes the use of low-level light therapy [10].

Although numerous clinical studies of low-level light therapy in treating acne vulgaris have been extensively conducted during the past decade [13, 31, 32], only three randomized controlled clinical studies have investigated at-home light-emitting diode devices for the treatment of acne [13, 23, 32]. Low-level light therapy uses either coherent light sources (lasers) or noncoherent light sources consisting of filtered lamps or light-emitting diode, or a combination of both. Laser diodes are the light source used in home devices for the treatment of alopecia diseases, such as androgenetic alopecia, female pattern alopecia, and alopecia areata; however, there have been no studies using home-based devices for acne treatment [33].

This prospective study showed that phototherapy with this novel, hand-held, blue light-emitting diode-red laser diode combined low-level light therapy device is a safe and effective treatment option for mild-to-moderate acne. After the 4-week treatment period, we observed significant decreases in inflammatory acne lesions, and these improvements were maintained for up to 4 weeks after the final treatment. At the final 8-week follow-up, substantial reductions of 64.7% and 59.3% in inflammatory lesions were observed in the per-protocol and intention-to-treat groups, respectively, without any serious side effects. Although the total dose of light irradiated to acne patients was much lower than that in previous studies on combination phototherapy, the overall improvement in inflammatory lesions was not inferior to that in earlier reports [13, 20–22, 34]. One study reported a significant reduction in inflammatory and noninflammatory acne lesions by 77% and 54%, respectively, in 35 light-emitting diode-treated patients for 2.5 min twice daily for 4 weeks [13]. Another randomized controlled trial demonstrated a significant improvement in acne lesion resolution compared with sham-irradiated treatment [31, 32]. In contrast to previous studies, we used laser diodes instead of light-emitting diodes as the red-light source.



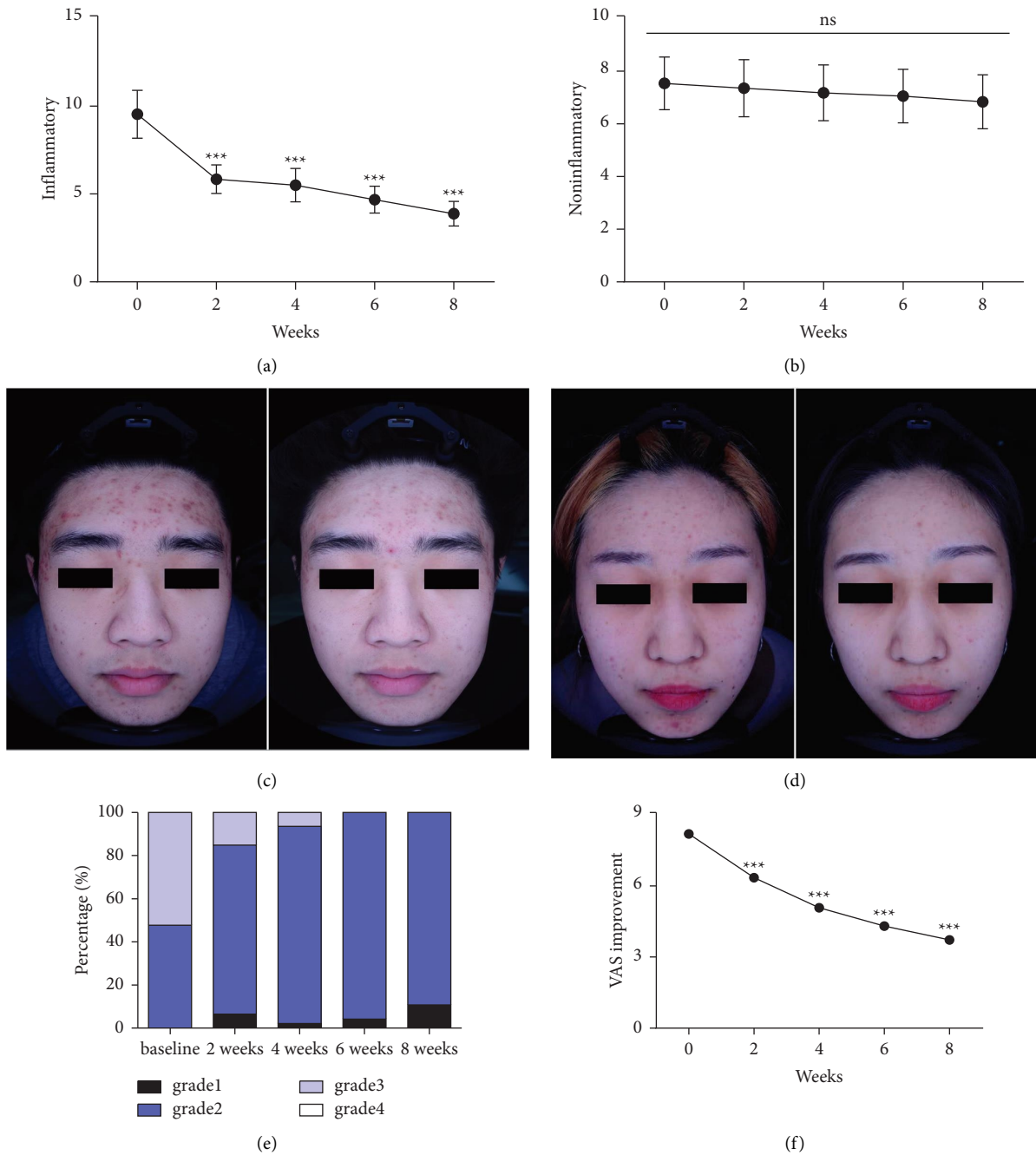


FIGURE 3: Treatment efficacy in the per-protocol population. (a) Changes in inflammatory acne lesion counts with time (\*\**p* < 0.001). (b) Changes in noninflammatory acne lesion counts with time. “ns” indicates that there is no statistical difference. (c) A 25-year-old male prior to treatments (left) and at 8 weeks following 4 weeks of light-emitting diodes-laser treatments (right). (d) A 27-year-old female prior to treatments (left) and at 8 weeks following 4 weeks of light-emitting diodes-laser treatments (right). (e) Number of patients with each grade of acne severity at each time point in the per-protocol population, graded using the Investigator’s Global Severity Assessment. (f) Changes in the patients’ subjective assessments of acne severity with time (measured by visual analogue scale) (\*\**p* < 0.001).

Previous studies have reported that laser diodes have better wound healing effects than light-emitting diodes [35]. Additionally, the clinical improvement in the study was comparable to that observed with the use of topical antibiotics and retinoids as the first-line treatment for mild-to-moderate acne. While topical antibiotics and retinoids cause antibiotic resistance and irritation, respectively, our patients

experienced no such side effects during the treatment and follow-up periods [36–38]. If further large-scale studies show similar effectiveness and safety, this blue-red combined low-level light therapy device could become a reliable and safe alternative for the treatment of mild-to-moderate acne.

Despite its effectiveness in various clinical settings, the mechanism underlying combined blue- and red-

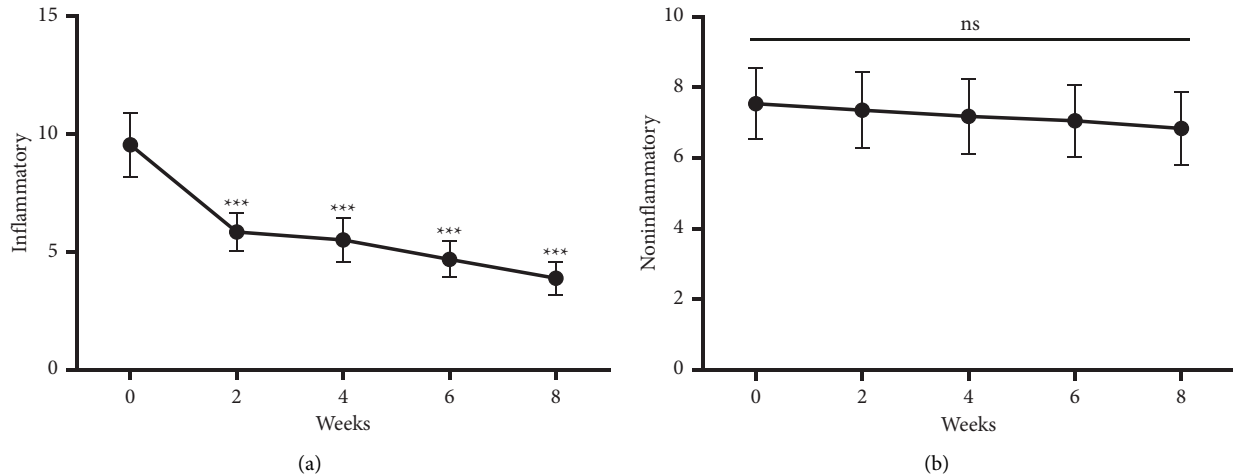


FIGURE 4: Treatment efficacy in the intention-to-treat population. (a) Changes in inflammatory acne lesion counts with time in the intention-to-treat population (\*\*\*)  $p < 0.001$ . (b) Changes in noninflammatory acne lesion counts with time in the intention-to-treat population. “ns” indicates that there is no statistical difference.

light irradiation has not been elucidated. Only a handful of authors have proposed possible mechanisms for this phenomenon. Blue light has been shown to activate coproporphyrin III and protoporphyrin IX, leading to the destruction of *Cutibacterium acnes* [14, 39–41]. Similarly, red light has been shown to be effective in accelerating wound healing and reducing the inflammatory response, possibly by stimulating mitochondrial activity and modulating the release of cytokines from macrophages [42, 43]. Kwon et al. proposed that the anti-inflammatory properties of mixed blue and red light may induce the suppression of activated NF- $\kappa$ B and activator protein 1 pathways [13].

We assumed that the reason for the substantial improvement despite treatment completion was mainly related to photobiomodulation, which initiates the excitation of endogenous chromophores to elicit photophysical and photochemical events [44, 45]. Although the exact mechanism associated with cellular photobiostimulation by low-level light therapy is not yet fully understood, low-level light therapy enhances collagen synthesis and fibroblast proliferation and promotes various growth factors and extracellular matrix production by activating cellular mitochondrial respiratory pathways [19, 45, 46]. The improvement of inflammatory acne lesions could have been sustained by the remodeling of the key epidermal and dermal components.

Although the bactericidal effect of light-emitting diode phototherapy depends on wavelength, power density, bacterial viable number, and bacteria species, it has been demonstrated to have an antibacterial effect. The bactericidal effect of blue light-emitting diode irradiation depends on the strains and conditions of bacterial inoculation; however, wavelengths of 425 and 525 nm have a bactericidal effect [47]. Similarly, de Oliveira Assunção et al. investigated the effect of wavelengths and energy densities of light-emitting diode irradiation, ranging from the blue (465 nm) to the red spectrum

(630 nm), which could suppress the growth of various bacteria, such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli* [48].

The limitations of this study are as follows: Since the device was designed for in-home use, safety issues associated with long-term use should be tested more rigorously in subsequent studies. In addition, given the absence of a control group or split-face design, our study is unable to rule out the potential effects of cleansers and moisturizers on acne reduction. Although the results of this study are promising, the optimal irradiation fluence and treatment regimen should be determined in future studies. Further studies are required to investigate the exact mechanism of this low-level light therapy device.

## 5. Conclusion

In conclusion, this study showed that this hand-held blue-red combined low-level light therapy device had beneficial effects on inflammatory acne lesions with excellent patient compliance and satisfaction. This device appears to be both safe and effective for the treatment of mild-to-moderate acne and could provide alternative strategies for treating acne against conventional acne treatments.

## Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Ethical Approval

All procedures performed in this study involving human participants were in accordance with the ethical standards of the Institutional and/or National Research Committee, and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.



## Conflicts of Interest

Sung Yul Lee and Jung Eun Kim have received a research fund from Ptech Corp., which provided LLLT devices used in the study. Euy Hyun Chung, Ji Won Son, Yun Su Eun, Na Gyeong Yang, Jae Yoon Kim, Sulhee Lee, Nam Hun Heo, Jinhui Rhee, and Yongsung Hwang declare that they have no conflicts of interest.

## Authors' Contributions

Euy Hyun Chung wrote the original draft. Ji Won Son provided the resources, performed data curation, performed formal analysis, performed investigation, and wrote the original draft. Yun Su Eun provided the resources. Na Gyeong Yang performed data curation. Jae Yoon Kim wrote, reviewed, and edited the article. Sulhee Lee contributed to visualization. Nam Hun Heo provided the software and performed formal analysis. Jinhui Rhee performed validation. Sung Yul Lee performed the methodology. Yongsung Hwang performed supervision, conceptualized the study, performed formal analysis, wrote the original draft, and wrote, reviewed, and edited the article. Jung Eun Kim performed project administration, performed supervision, conceptualized the study, performed formal analysis, wrote the original draft, and wrote, reviewed, and edited the article. Euy Hyun Chung and Ji Won Son contributed equally to this study.

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## Supplementary Materials

Supplementary Figure Legends. Figure S1: P1-FOX (PAD-FA120; Ptech Corp., Pyeongtaek, Korea). Supplementary Tables. Table S1: Lists of primers used in the study. Table S2: Investigator's Global Severity Assessment. (*Supplementary Materials*)

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