Possibilities and limitations of using various light sources in the treatment of acne vulgaris

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ABSTRACT

Acne vulgaris is a chronic inflammatory skin condition with a high global prevalence. Light-based therapies can be used in acne treatment on account of their good safety profile, lack of potential for developing resistance, and mechanism of action. Despite variations in research methodologies and diverse findings among researchers, numerous clinical studies have shown a statistically significant improvement in the skin condition of acne patients treated with light. In the majority of studies, the follow-up period is comparatively short, preventing the evaluation of long-term effects of therapy. This paper examines the literature on the effects of various light therapies (based on LED devices, photodynamic therapy, intense pulsed light, and laser therapy), on the clinical signs of acne.

Key words: lasers, light, phototherapy, acne vulgaris.

INTRODUCTION

Acne vulgaris is a chronic inflammatory condition involving pilosebaceous units, characterized by a complex pathogenesis. The primary factors contributing to the formation of acne lesions include seborrhea, hyperkeratosis of follicular openings resulting in the formation of keratotic plugs (comedogenesis), colonization of sebaceous glands by *Cutibacterium acnes*, and inflammation [1]. Acne treatment can be challenging due to the complex etiology of the disease, rising antibiotic resistance, and their potential for adverse drug reactions. Lately, there has been a growing interest in the experimental treatment of acne with light, based on the efficacy and high level of safety associated with this therapeutic modality [2]. Phototherapy can be used either alone or in conjunction with pharmacological treatment [3].

A broad spectrum of electromagnetic radiation can be used in the treatment of acne, including ultraviolet radiation (UV), visible light, and infrared radiation (IR). Light sources include lasers, halogen lamps, fluorescent lamps, and light emitting diodes (LED).

In response to light absorbed by chromophores present in the skin, numerous photochemical reactions occur, mainly resulting in bactericidal activity. Porphyrins produced by bacteria primarily absorb wavelengths within the blue light range. By using phototherapy with deeper-penetrating wavelengths (green, yellow, red, and infrared light), it is possible to directly target the sebaceous glands to induce a localized anti-inflammatory effect. The phototoxic effect on the sebaceous glands leads to a reduction in their size and decreases the secretion of sebum. Energy absorption by *Cutibacterium acnes* inhibits the synthesis of bacterial DNA and the production of compounds toxic to bacteria during the oxidation process. As a result, inflammation subsides and normal keratinization, disrupted by bacterial colonization, is restored [3].

LIGHT-EMITTING DIODE (LED)

LED is a complex of semiconductors with the capability to convert electric current into a non-coherent beam of light with a narrow spectrum. LEDs used for medical purposes can emit light across a range of wavelengths, spanning from ultraviolet, through visible light, to near-infrared (NIR). The biological effect is attained through the emission of photons that are absorbed by chromophores (also referred to as photoacceptors), including mitochondria or cell membranes. Photomodulatory effects on respiratory chain proteins lead to increased ATP production in fibroblasts, inhibition of apoptosis, stimulation of angiogenesis and blood flow, and modulatory activity on cytokines [4].

Blue light (400–500 nm) has low penetrability and can be employed for treating pathological processes within the epidermis. Yellow light (approximately 540 nm) is used for the treatment of red skin, edema or skin pigmentation disorders. Red light (620–700 nm) penetrates deeply into the dermis and activates fibroblasts, while monochromatic light (700-1200 nm) achieves the deepest penetration, stimulating the process of angiogenesis [4].

LED THERAPY IN THE TREATMENT OF ACNE VULGARIS

Blue light (400–500 nm)

Blue light is known to inhibit bacterial growth. Due to the effects of radiation, photodynamic reactions occur in endogenous chromophores, disrupting the integrity of pathogen cell membranes and transmembrane ion transport. As a result, the proliferation of *C. acnes* is constrained [5]. Because of the great challenge posed by growing antibiotic resistance, blue light phototherapy is increasingly becoming the treatment of choice, given its multidirectional antimicrobial activity and safety [5, 6]. In their 2015 study, Asha *et al*. used 414 nm blue light emitted from a LED device to assess its therapeutic efficacy in 41 patients with acne. Photographic documentation was done every 2 weeks over the course of 12 weeks. A 50.02% decrease in inflammatory lesions was observed in the study group (26 subjects), compared to a 2.5% improvement in the control group (15 subjects). No adverse effects or pain were reported [6]. In contrast, Tzung *et al.* in their study (involving two irradiation treatments per week, exposure to light at a wavelength of 420 nm at a dose of 40 J/cm^2, for a period of 4 weeks) observed an exacerbation of nodulocystic acne lesions despite an improvement in papulopustular lesions in 52% of the subjects [7]. In their randomized clinical trials, Arruda *et al*. and Cheema *et al*. compared blue light therapy with the topical application of benzoyl peroxide at concentrations of 5% and 4%. The outcomes of both studies showed blue light to have superior efficacy in reducing acne lesions, with fewer adverse effects [8]. There are literature reports of various blue light sources, including lasers and LEDs, employed for therapeutic purposes. In the study by Masson-Meyers *et al.*, both sources were found to have comparable efficacy [9].

Red light (620–700 nm)

Red light penetrates more deeply into the skin than blue light, restricting sebum production in the sebaceous glands. Moreover, red light has been observed to inhibit the release of prostaglandins E2 (PGE2). An *in vitro* study of red light therapy administered at low doses (0.2–1.2 J/cm^2) found that the treatment can be effective in acne management by reducing seborrhea, relieving inflammation, and improving the skin's natural barrier function [10]. In the study conducted in 2007 by Na and Suh, radiation in the range of 635-670 nm was applied to one half of the facial skin of the patients for a total of 15 minutes, twice daily, over an 8-week period. The cumulative dose at the conclusion of the study was 604.8 J/cm^2. The other half of the face was untreated. The mean reduction in inflammatory and non-inflammatory lesions on the treated side reached 55%. No significant adverse effects were reported [11]. In contrast, a study comparing the therapeutic effects of red light (630 nm at 48 mW/cm^2) and blue light (405 nm at 30 mW/cm^2) found blue light therapy to have superior efficacy in acne treatment [12].

PHOTODYNAMIC THERAPY

Photodynamic therapy (PDT) is based on a combination of visible light and a topical photosensitizing agent. The most commonly employed photosensitizing agent is 5-aminolevulinic acid (ALA), acting as a precursor to protoporphyrin IX, which is the actual photosensitive compound. Protoporphyrin IX releases reactive oxygen species, including singlet oxygen and free radicals, leading to the destruction of sebaceous gland cells and producing a direct toxic effect on *C. acnes*. ALA is rapidly eliminated from the body, which mitigates its harmful effects on healthy tissue. Adding a methyl group to ALA results in the formation of methyl aminolevulinate (MAL), which is characterized by increased lipophilicity. Because of this chemical property the photosensitizing compound selectively accumulates in the sebaceous glands, which minimizes its adverse effects in other skin structures [13, 14]. Other derivatives of porphyrins, chlorins and bacteriochlorins are also used as photosensitizers in PDT. The new class of photosensitizing agents includes indocyanine green and indole-3-acetic acids [15]. The optimal contact time between the photosensitizer and the skin is 15–90 minutes [16].

Calzavara-Pinton *et al*. used red light therapy (635 nm) at a dose of 37 J/cm² in combination with MAL. Over 75% of the 221 study subjects experienced an improvement in acne lesions, with an average reduction of 72.8% [17]. Bissonnette *et al*. compared two radiation doses (35 J/cm² and 27 J/cm²), demonstrating superior efficacy of the higher dose in the treatment of acne lesions [18]. Photodynamic therapy can also be performed with intense pulsed light (IPL). IPL is highly effective in PDT, with the average reduction in acne lesions of approximately 72%. The benefits are similar to red light therapy, but with IPL it takes longer to achieve the therapeutic effect. In clinical practice, low doses of radiation, in the range of 7–10 J/cm², are used [19, 20]. In several clinical studies, lasers were also employed as a light source, including PDL (pulsed dye laser) and LPDL (long-pulsed dye laser). However, the outcomes of the studies varied considerably, preventing definitive conclusions [21].

INTENSE PULSED LIGHT

Technically speaking, intense pulsed light (IPL) is not a laser, as it does not produce a coherent beam of monochromatic light. Instead, it generates scattered polychromatic radiation beams of different wavelengths (in the 400–1200 nm spectrum) that affect various layers of the skin. IPL is administered using flashlamps and diverse cutoff filters, enabling the precise wavelength to be achieved while eliminating others. In the treatment of acne, filters are employed to achieve wavelengths around 420 nm. Emitted light is absorbed by porphyrins present in *C. acnes*, but also by endogenous chromophores that are present in the skin, which consequently leads to the destruction of blood vessels supplying the sebaceous glands. Moreover, IPL has anti-inflammatory properties by influencing the activity of TNF and TGF-β [3]. Kumaresan and Srinivas compared the therapeutic efficacy of multiple pulses (5 pulses every 6 ms) with single pulses (every 12 ms). Treatment with multiple pulses (reduction –56.66%) versus single pulses (40.17%) was found to be more effective [22]. A study involving 50 patients revealed no statistical difference between IPL used for acne treatment in monotherapy (530-nm filter, 35 J/cm², individual pulses of 35 ms) and the application of 5% benzoyl peroxide (BPO) once daily [23]. In the management of acne, both monotherapy and combination therapy, incorporating topical formulations including 5% BPO and retinoids, have proven to be effective [24].

Laser therapy of acne

The word 'laser' is an acronym for Light Amplification by Stimulated Emission of Radiation. This implies that the observed effect is attained through the phenomenon of stimulated emission of photons which generate a wave of the same length and consistent phase. Laser-emitted light is differentiated from light from other sources by beam characteristics such as coherence, monochromaticity, and parallelism (collimation). These properties make it easier to focus the beam in a small area and achieve high irradiance. In dermatology, the most important benefits of laser therapy are due to the photothermal and photochemical effects of laser on tissues [25, 26].

KTP laser

Potassium-titanyl-phosphate (KTP) laser, which uses $KTiOPO_4$ as the lasing medium, emits green light at a wavelength of 532 nm. KTP laser is fre-

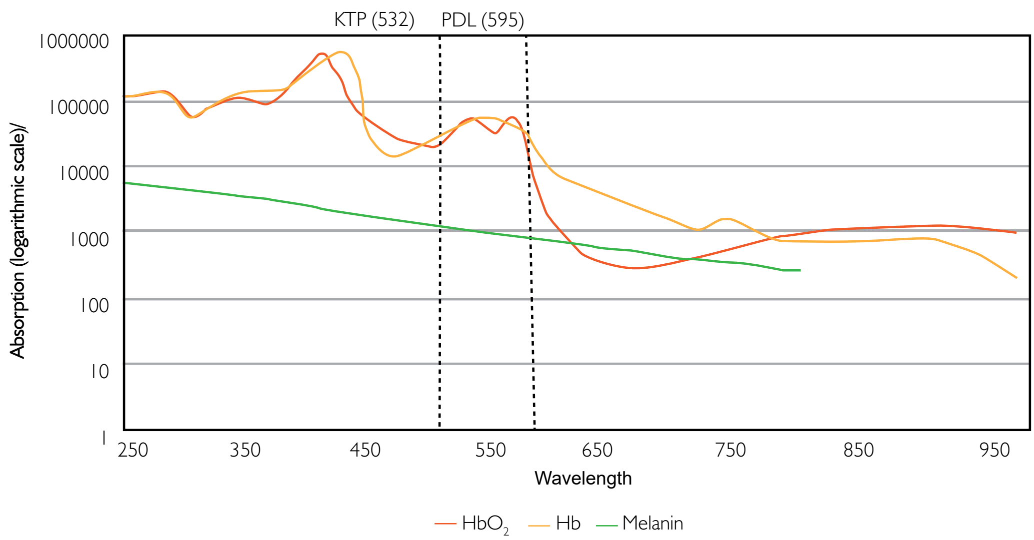

Figure 1. Absorption of radiation by chromophores as a function of wavelength. KTP and PDL laser wavelengths marked

quently employed for the removal of vascular lesions, as oxyhemoglobin and melanin are chromophores for wavelengths in this range (fig. 1). The precise mechanism through which acne lesions are reduced remains unknown. It is hypothesized that the effect is achieved via selective photothermolysis of blood vessels and sebaceous glands. In addition, porphyrins produced by *C. acnes* absorb green light and, through the process of photoactivation, release oxygen free radicals that exert a destructive effect. KTP laser therapy is considered safe; however, transient side effects such as erythema, edema, or epidermal exfoliation may occur after treatment. In individuals with darker skin phototypes, treatment may cause post-treatment hyperpigmentation. Yilmaz *et al*. conducted a comparison study by administering therapy with KTP laser at 532 nm (dose: 5–12 J/cm^2; pulses: 20–40-ms) to one half of the face in 38 patients with acne and leaving the other side untreated. The authors noted a 40% reduction in acne lesions on the treated side compared to a 13% reduction on the other part of the face [27].

Dye laser

Dye laser uses a fluorescent organic dye, usually as a liquid solution, as the lasing medium. Pulsed dye laser (PDL) was initially used for the treatment of vascular lesions, as it emits wavelengths in the yellow light portion of the spectrum (585 nm and 595 nm), which correspond to the absorption peak of oxyhemoglobin (fig. 1). In recent years, PDL has also been used to treat inflammatory lesions, including acne. This occurs because hemoglobin absorbs a specific wavelength, leading to a local increase in temperature in blood vessels and the release of anti-inflammatory cytokines. Moreover, wavelengths in the range of 585–595 nm are absorbed by porphyrins produced by *C. acnes*. PDL also triggers an increase in TGF-β, resulting in increased collagen synthesis and thereby reducing the risk of acne scarring. In addition, PDL yields beneficial effects in reducing the number of comedones [28]. The effect can be amplified through the simultaneous use of the Nd:YAG laser, which penetrates into the deeper skin layers, causing damage to over-reactive sebaceous glands. Salah el Din *et al*. evaluated treatment with PDL (585 nm, dose: 7–9 J/cm^2, pulse duration: 40 ms, spot size: 7 mm) and Nd:YAG laser (1064 nm, dose: 40–50 J/cm^2, pulse duration: 40 ms, spot size: 7 mm) [28]. PDL laser therapy may induce discomfort, and after treatment, there is a potential risk of purpura and skin pigmentation disorders. Such effects, however, are transient in nature. Special care should be exercised in the therapy of patients with darker skin phototypes, who are at an increased risk of hyperpigmentation [29].

Nd:YAG laser (1064 nm)

Neodymium-doped yttrium aluminum garnet (Nd:YAG) laser can be powered either by pulsed flashlamps or diode laser. Nd:YAG devices emit a beam with a wavelength of 1064 nm, falling within the infrared spectrum. These parameters correspond to peak water absorption (fig. 2), which is associated with a low degree of penetration into the skin. Also, this specific wavelength is absorbed by melanin and oxyhemoglobin.

The therapeutic effect on acne lesions is achieved through selective photothermolysis of blood vessels, increased secretion of TGF-β, decreased IL-8 levels, and thermal damage to sebaceous glands. These effects probably contribute to a reduction in non-inflammatory lesions, such as comedones [30]. A study conducted by Mohamed *et al.* showed that three sessions of Nd:YAG laser therapy (1064 nm) ev-

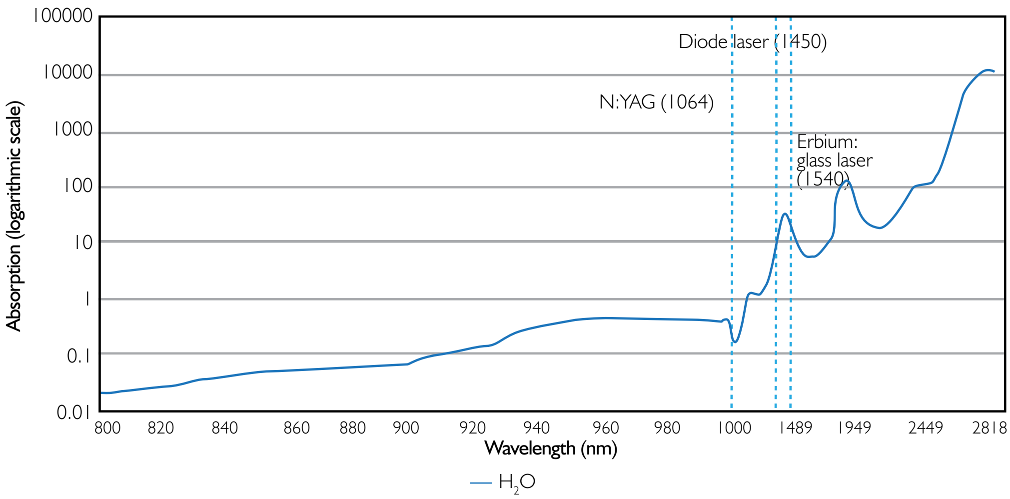

Figure 2. Absorption of radiation by water as a function of wavelength. Nd:YAG, diode laser, and erbium:glass laser wavelengths are marked

ery 4 weeks led to a reduction in acne lesions of up to 70.2%. The application of IPL therapy to the other half of the subjects' faces demonstrated no statistically significant difference in efficacy [31]. In another study, involving 34 participants with mild to moderate acne symptoms, the therapeutic efficacy of 1064-nm Nd:YAG treatment administered to one half of the face (5-ms pulses at a dose of 30 J/cm^2; spot size 7 mm) was compared to 595-nm PDL applied to the other facial half (10-ms pulses at a dose of 8.5 J/cm^2; spot size 7 mm). Both lasers had a positive treatment effect, with no statistically significant differences in efficacy. The patients showed a preference for Nd:YAG laser treatment due to experiencing less discomfort during therapy [30]. A long-lasting reduction in acne lesions (follow-up after 12 months) was noted in a study comprising eight sessions of Nd:YAG laser therapy (long pulses: 60 ms, dose: 20–23 J/cm^2, spot size: 10 mm) and the QS mode (dose: 1.1–1.3 J/cm^2, spot size: 6 mm). The overall improvement was estimated at 84% [32].

Diode (semiconductor) laser (1450 nm)

Treatment with diode laser, emitting radiation in the infrared spectrum (1450 nm), also has applications in dermatology. This wavelength allows deep penetration into the dermis, where the sebaceous glands are located. In this acne treatment modality, the goal is to induce thermal damage to over-reactive sebaceous glands and hyperkeratotic infundibulum cells, which supports long-term management of the condition. Furthermore, a bacteriostatic effect is observed, with radiation affecting the composition of sebum which serves as a nutrient source for *C. acnes* bacteria. Concurrent application of cooling gels minimizes the risk of damage to the epidermis and the development of adverse effects, such as redness, swelling, or skin hyperpigmentation. The first clinical trial exploring the applications of diode laser in acne treatment was conducted by Friedman *et al.*, who employed diode laser at a dose of 11–14 J/cm^2 in 19 patients in three sessions performed every 4 to 6 weeks. A reduction in skin lesions of up to 86% was observed, with adverse effects manifested only by transient redness and swelling [33]. Doubts about the efficacy of diode laser therapy were raised in the study by Darnè *et al.* in a group of 32 patients, in which no difference was observed between the laser-treated face half and the non-treated control half [34]. To minimize damage to surrounding tissues, attempts were undertaken to introduce light-absorbing chromophores directly into the glands. Paithankar *et al.* used gold-coated silicone particles absorbing 800 nm radiation at a dose of 10–50 J/cm^2, with 30-ms pulses. Twenty-eight days after completing the therapy, which consisted of three irradiation sessions, a 61% reduction in inflammatory lesions was noted [35]. Lloyd and Mirkov conducted a clinical trial using indocyanine green as a chromophore to facilitate selective photothermolysis of hyperreactive sebaceous glands. The therapy involved radiation delivered in 50-ms pulses, at 810 nm, at a dose of 40 J/cm^2. Histological examination revealed selective necrosis of sebaceous glands. Clinical improvement in the skin condition of patients was also observed at follow-up visits after 3, 6 and 10 months [36].

Erbium:glass laser

The device emits light with a wavelength of 1540 nm, which corresponds to the mid-infrared range. Erbium:glass laser has a water absorption peak in its spectrum (fig. 2), which results in selective damage to various water-containing structures, including keratinocytes, collagen, or blood vessels. This, in turn, activates processes such as epidermal repair and collagen remodeling. The effects outlined above lead to a sensation of tightness and dryness in the skin. Consequently, laser sessions should be followed by skin hydration treatment. Acne therapy relies on the process of energy absorption by sebaceous glands in the skin, resulting in their damage through a photothermal reaction. A positive effect of therapy is the reduction of seborrhea in patients [37]. This observation was documented in a clinical study of 25 patients conducted by Angel *et al*. In this study, an average lesion reduction of up to 71% was noted in the subjects after four courses of treatment (cumulative dose: 40 J/cm^2, 3-ms pulses) at a dose of 10 J/cm^2, administered every 4 weeks. Post-treatment skin biopsy revealed a decrease in the size of sebaceous glands without morphological damage to structures in the skin or epidermis. Erbium:glass laser treatments are considered safe, as reported in clinical trials where patients experienced only transient erythema and edema. The application of cooling agents was found to additionally reduce the risk of thermal damage to the surrounding tissues [38]. High efficacy of erbium:glass laser therapy was also shown in a study involving 45 patients who underwent four treatments (spot density: 169/cm^2, wavelength: 1550 nm, dose: 15–30 mJ/cm^2) every 4 weeks. Immediately after the sessions, a 67.7% reduction in acne lesions was observed. After year, the mean reduction in lesions reached 79%, and after 2 years 75%. All patients reported a reduction in seborrhea [37].

CONCLUSIONS

Contemporary treatment of acne is based on a variety of topical and oral agents that target specific components of the pathogenesis of acne lesions. The pursuit of innovative acne treatments is mainly driven by the incomplete efficacy of external therapies and their potential for adverse effects, such as skin irritation in topical treatments or teratogenicity during isotretinoin therapy.

The authors of the European Dermatology Forum (EDF) guidelines are of the view that blue light monotherapy could be considered for the treatment of mild to moderate papulopustular acne. However, it needs to be stressed that the strength of these recommendations is low. In addition, the guidelines neither endorse nor discourage the use of red light, IPL, lasers, and PDT for the therapy of severe papulopustular acne and moderate nodular acne because there is no adequate evidence regarding the effectiveness of these therapies, while the shortage of clinical data prevents the adoption of standardized management guidelines. Furthermore, monotherapy with visible light is not recommended in patients with severe nodular acne, while treatment with ultraviolet radiation from artificial sources is not advised for any type of acne [39]. The 2019 EDF guidelines on photodynamic therapy in dermatology recommend the application of PDT (at I B level), while underlining the need to standardize treatment protocols [40].

Acne is a condition with a multifactorial pathomechanism, which markedly complicates the selection of a control group. The clinical trials conducted to date have not consistently considered factors such as disorders of hormone metabolism, exposure to external elements (e.g. sunlight), dietary habits, genetic background, or cosmetics used in daily skincare, which could have impacted the reliability of the study findings.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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