The effect of light in the treatment of acne vulgaris

A ação da luz no tratamento da acne vulgar

Review Article

ABSTRACT

For several years, the treatment of acne vulgaris has been based on the use of oral or topical medication, isolated or in association with other medications. Such options still represent excellent therapeutic alternatives; however, there are cases in which they cannot be used either because of their side effects or the lack of response to treatment due to the growing bacterial resistance to antibiotics. Based on the observation that light has been successfully used to treat many pathologies – including acne – a number of therapeutic devices have been developed that demonstrate good results. The objective of this article is to present a review of the pathology of acne and of the photobiological principles used in its treatment, considering some of the main current phototherapeutic modalities.

Keywords: acne vulgaris; phototherapy; laser therapy

RESUMO

Durante vários anos o tratamento da acne vulgar tem-se baseado no uso de medicamentos orais ou tópicos, isolados ou usados de forma associada. Embora ainda representem, em sua maioria, excelentes opções terapêuticas, há casos em que essas inúmeras opções não podem ser usadas, seja por seus efeitos colaterais ou falta de resposta ao tratamento observada com a crescente resistência bacteriana aos antibióticos. Na tentativa de buscar novas opções terapêuticas e com base no fato de a luz ser utilizada com sucesso no tratamento de diversas doenças, a acne entre elas, inúmeros dispositivos foram desenvolvidos para esse fim com bons resultados. Este artigo tem por objetivo fazer uma revisão da fisiopatologia da acne, bem como dos princípios fotobiológicos aplicados em seu tratamento e aborda algumas das principais modalidades fototerápicas atuais.

Palavras-chave: *acne vulgar; fototerapia; terapia por laser*

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INTRODUCTION

Acne vulgaris, a chronic pathology of the sebaceous glands has multiple causes, and a high prevalence. Approximately 80% of all people will develop it sometime in their lifetime [1], which represents more than 30% of dermatologic consultations each year [2,3]. It is a highly stigmatizing disorder that affects mainly young people, which may induce phobias and social isolation, and in some cases, depression and suicide [4,5].

Currently there are countless drug-related therapies, including retinoids and antibiotics (oral and topical), in addition to exfoliating substances, used in combination or alone. Treatment success depends largely on patient

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compliance with the therapeutic regime; however, prolonged use of antibacterial agents can impede progress by encouraging resistant strains of bacteria, especially *Propionibacterium acnes (P. acnes)*[6,7].

Although generally safe, drugs used to treat acne can involve side effects. For example, minocycline has been associated with autoimmune hepatitis, lupus erythematosus, and benign intracranial hypertension [8,9]. Oral isotretinoin, used with success mainly in cases of severe acne, may cause teratogenicity, mucous cutaneous symptoms, myalgias, and depression [10,11], in addition to elevated transaminases and lipids Based on the improvement of acne after solar exposure described by many patients [12], several studies were conducted in order to identify which wavelength is linked to the improvement described – if it is the ultraviolet, the visible light, or both [13] – and whether such improvement can be confirmed by clinical studies.

In an attempt to discover new therapeutic options to meet the increasing demand for fast and safe therapies with minimal side effects, some companies have developed light-based devices (with or without the use of lasers) as an alternative to pharmaceutical therapies [14].

This article's objective is to review acne's photobiological principles and discuss phototherapeutic modalities for its treatment.

PHYSIOPATHOLOGY OF ACNE

Recent discoveries about the physiopathologic mechanisms of acne have encouraged more effective therapies. Acne is a chronic and inflammatory disorder of the pilosebaceous follicle, constituted by a large and multilobulated sebaceous gland, hair and wide follicular channel, covered by stratified squamous epithelium [15].

Although the pathogenesis of acne has not been completely explained, four factors are studied exhaustively: (1) obstruction of the hair follicle, secondary to the abnormal desquamation of the follicular keratinocytes; (2) increase in sebaceous production; (3) proliferation of the anaerobic bacterium *P. acnes* – a relevant factor in the present article; and (4) immune and inflammatory reactions triggered by *P. acnes*.

In normal sebaceous follicles, the follicular keratinocytes are shed as isolated cells and carried out from the lumen through the fat secreted by the sebaceous glands [15, 16]. In patients with acne, keratinocytes desquamate in highly dense clusters, which act like a lid that obstructs the follicular infundibulum. This alteration is believed to be associated with changes in the sebaceous composition (for instance, a reduction levels of linoleic acid), defects in the androgen-controlled cellular proliferation, or high interleukin concentrations 1a (IL - 1 a) expressed by the follicular keratinocytes [16]. When these factors are present, a microcomedone is formed [16,17]. This small structure blocks the flow of fat, which obstructs the follicle and causes the accumulation of cellular fragments, bacteria, and lipids [18] in the follicular lumen. Many patients with acne have sebaceous follicles that are larger and more lobulated than normal [16]. It is believed that the increase in the production of fat is due to the increase of circulating androgen, a higher responsiveness of the gland to androgen, or both [19]. The 5 a-hydroxytestosterone and the 17 b-hydroxysteroid dehydrogenase are involved in such control; the keratinocytes and sebocytes are capable of metabolizing them [16].

Although acne is not exactly an infectious disorder, *P. acnes* has an important role in its pathogenesis, colonizing the follicles that present an appropriate microenvironment (anaerobic and rich in sebaceous material) for its survival 16. Although there is no consistent direct correlation between the density of *P. acnes* on the surface of the skin and the severity of the acne [20], the improvement observed with antibiotic therapy, and the lack of improvement in cases of antibiotic-resistant *P. acnes* [21], provide clear evidence of its physiopathologic importance.

After the follicle has been colonized by *P. acnes*, an inflammatory cascade is prompted by countless immunological mediators, leading to the rupture of the follicular wall, with the extravasation of lipids, keratinocytes and bacterial antigens [15 -17]. Chemotaxis substances from neutrophils, monocytes, lymphocytes, and pro-inflammatory cytokines such as the IL-8 and the tumorous necrosis alpha factor, produced by macrophages, besides the complement system take part in this process. [15, 17, 19]. The activation of this inflammatory cascade, associated with the rupture of the follicular wall and the liberation of lipids with bacterial residues perpetuates the inflammatory process.

PHOTOBIOLOGICAL PRINCIPLES

The key to the development of any light-based therapy is figuring out how to deliver its energy to the cutaneous structures in an effective and highly selective manner, while minimizing damage to the surrounding tissue.

Although this article does not intend delve into the physical principles governing phototherapy, some definitions are fundamental for understanding the subject.

Optical tissues are the target-specific structures of the skin that receive the energy of the photons. Photobiological reactions are the biological processes that happen after the absorption of this energy by the skin [22].

When the light hits the skin, three processes of interaction between the photon and the tissue structures may happen: reflection, dispersion, or absorption [22]. The depth of the light's propagation depends on how much it is dispersed by tissular structures along its path. In the case of ultraviolet, visible light, and infrared, this process is wavelength dependent – longer wavelengths penetrate more deeply than shorter ones [22].

The absorption process is most relevant for this discussion, since it allows the transfer of the energy of the light to the tissue. Without the absorption process, the energy of the photons is not transferred to the specific structures and no biological or therapeutic effect takes place. As with the dispersion process, absorption is also wavelength dependent,

though in more complex way [22].

The light that is reflected by the skin is noticed by the human visual system; however, as that light is dispersed, it does not result in any therapeutic effect. The molecule responsible for the absorption of the light's energy is denominated chromophore. Any biological process starts with the interaction of the light with a specific chromophore – each has a unique absorption spectrum. The excitement of the chromophore during absorption induces chemical reactions and the formation of a photoproduct [23]. In human skin there are chromophores that are photodynamicly active and photo unstable substances [24]. Currently numerous chromophores – such as melanin, water, exogenous pigments, and photosensitizing drugs (psoralens and photosensitizers - Photodynamic therapy) [22] – are employed in several phototherapeutic modalities. In the acne case, although the abundance of fat, the presence of bacteria, and the hypervascularization of the inflamed areas contribute to the potential selective damage of the lesions in the skin, apparently there is not a single chromophore associated with the condition. In acne, as in other disorders where phototherapy can be used, the presence of specific target chromophores is fundamental.

As described previously, the presence of *P. acnes* in the sebaceous follicles is intimately associated with the development of inflammatory acne [23 24]. As part of its normal metabolic process, this Gram-positive and microaerophilic bacterium synthesizes porphyrins (mainly protoporphyrin and coproporphyrin), photosensitive substances [25] that interfere in cellular chemical and metabolic reactions when they absorb the light's energy. When the light is absorbed by the porphyrins, reactive types of oxygen (free radicals) [26] – which inactivate the *P. acnes* without triggering the induction of bacterial resistance – are formed.

The porphyrins' spectrum of absorption is around of 400 nm, with the highest light absorption peak ("Soret Band") usually in the blue and violet band (415 nm); devices employing this wavelength were therefore

developed for treating acne. The visible spectrum of the porphyrins also displays several weaker absorption peaks ("Q-Bands") in longer wavelengths [23].

PHOTOTHERAPEUTIC MODALITIES

The main light-based therapeutic modalities used in the treatment of acne vulgaris are described below.

PHOTODYNAMIC THERAPY

Based on the knowledge that *P. acnes* contains endogenous porphyrins that are fluorescent substances and that acid 5-aminolevulínico (ALA) induces fluorescence selectively in the pilosebaceous unit, photodynamic therapy (PDT) was introduced as a treatment for acne [13].

An *in vitro* study demonstrated that ALA is metabolized in the pilosebaceous unit into protoporphyrin IX. The latter in turn accumulates mainly in the sebaceous gland, and in the hair follicle and epidermis in smaller amounts. The irradiation of this chromophore with the appropriate wavelength destroys the sebaceous gland and may hurt the follicles and the epidermis [27]. Therefore, the metabolization of the ALA inside the pilosebaceous unit, resulting in the formation of protoporphyrin IX (synthesis path of the heme) and its subsequent photoactivation, has the potential of damaging the sebaceous glands and photoinactivating the *P. acnes* [27]. In addition, more liposoluble ALA esters were developed that achieved a higher penetration in the pilosebaceous unit and the *P. acnes* [28].

Hong Choru and others applied ALA-based creams with 20% concentration [29] to patients (n = 22) with moderate acne on the trunk 3 hours before treatment with 550-770 nm wavelength (Broadband) and 150 J/cm2 of energy. The sessions were repeated 4 times. The authors observed a reduction in the size of the glands, in the fluorescence of *P. acnes*, and in the production of fat. Clinical improvement was maintained for up to 20 weeks. A subsequent study demonstrated clinical improvement of facial acne with 20% ALA-PDT in low doses. The ALA was applied 4 hours before irradiation treatment with both Excimer Dye LASER (635nm, 5 J/cm2) and a Broadband halogen source (600-700nm, 13J/cm2). Improvement was sustained up to 8 months after a single treatment [30].

In spite of the excellent clinical results observed with ALA-PDT, side effects include transient hyperpigmentation, discomfort during treatment, superficial exfoliation, erythema, and the formation of crusts [31, 32].

UVA and UVB radiation

Although solar exposure is described by several patients as beneficial in controlling acne, it is not known which wavelength is responsible for this improvement: UV, visible light, or both. Treatment with UVA/UVB seems to have little beneficial effect on acne, and its carcinogenic effects are well known [33].

Several studies demonstrate that the *in vitro* viability of *P. acnes* is inversely proportional to the intensity of the light. In this manner, *P. acnes* sensitivity is higher for shorter wavelengths [34]. Other experiments show that *P. acnes* can be inactivated *in vitro* by relatively small energy doses (D10=5KJ/m2) of UV radiation Broadband, and that this phenomenon is oxygen dependent [35].

Another interesting observation is the dose-dependent relationship between light and the lymphocytes: high intensity UV has a lymphocytotoxic effect, and can reduce the inflammatory reaction; low intensity light can stimulate inflammatory reactions [36, 37]. Yet in relation to the immunological aspect, another study has showed that UV radiation can induce alterations in the comedone cytokines (IL10 and IL1) in patients with acne [38].

Although UVB has the potential of killing *P. Acnes* in *in vitro* experiments, high doses would have to be applied in order to penetrate the skin, which would not be clinically justified due to the risk of burns [39, 40]. Studies conducted by

Mills and Kligman [41] question the efficacy of UV radiation applied in vivo. Initially using intense UVB radiation for the treatment of acne comedones in the dorsum, they did not observe any improvement in the lesions, except for an intense desquamation of the skin. A second study by the same authors evaluated several UV modalities for the treatment of papulopustular acne of moderate to severe grades; UVB, UVA and a combination of both were compared. The number of comedones was significantly reduced, and the combination UVA/UVB treatment produced only minor improvement in the inflammation [41].

New studies would be necessary to analyze the therapeutic action of UVA and UVB. However, the little improvement observed may not justify its use due to its potential carcinogenic risk [42, 33].

LASERS

Lasers are defined as sources of coherent light that can be focused on reduced tissue areas, providing a great intensity of energy. Considering that in dermatology most lasers are used for their capacity to heat the skin, its optimization depends on parameters such as wavelength, pulse duration, [43] and the capacity to cool simultaneously after application. The control of these parameters has been increasing the efficacy and safety of these devices, particularly for their capacity to reach selectively larger and deeper structures such as larger caliber blood vessels and hair follicles [22].

A randomized double-blind study evaluated 41 patients with light to moderate inflammatory acne after a single treatment with pulsed Dye Laser with the following parameters: 585 nm, 5 mm spot size and 358 ms pulse. The patients were randomly distributed to receive 1.5 J/cm^2 on one side of the face and 3.0 J/cm^2 on the opposite side, and were evaluated after 2, 4, 8 and 12 weeks. At 12 weeks after a single application, significant improvement of the lesions was observed, with a reduction of 50% in their total count. No significant adverse effects were observed [44].

Although additional studies are necessary, some preliminary results suggest that lasers – specifically the pulsed Dye Laser, in this case – used on their own or combined with conventional medicines can be an effective therapeutic option for the treatment of acne.

THE USE OF BLUE LIGHT

Phototherapy with visible light has a beneficial effect on acne, and avoids the potential risks of long-term UV radiation exposure [34, 40]. Visible light's blue band has a photodestructive effect on *P. acnes* that could partly explain the decrease in acne severity described by some patients in the summer. It is currently known that the blue-violet light (405-420 nm) is 10 times more effective than the red light in unchaining the excitation of the coproporphyrins [45]. It has also been demonstrated that the irradiation of *P. acnes* with UVA and blue light induces alterations in the intracellular pH, affecting the transmembrane influx of proteins, causing damage to this bacteria [46]. The irradiation of *P. acnes in vitro* colonies with visible blue light leads to the photoexcitation of the endogenous bacterial porphyrins, production of singlet oxygen and the subsequent destruction of this bacterium 52.

Ashkenazi et al [47] cultivated *P. acnes* anaerobically for 72 hours in a liquid medium, irradiating the suspension 2 times, for 60 minutes, with an interval of 24 to 48 hours. They used intense narrow-band light, in the blue-violet band (405-420 nm), free from UV, with 20 mW/cm2 (total dose of 75 J/cm2). The viability of the treated culture decreased by 4 orders of magnitude when compared to the non-treated control bacteria.

Meffert et al [48] described the improvement of acne and seborrhoea in the backs and faces of male volunteer patients when using halogen bulbs that emit visible light, after 17 irradiations with an accumulated dose of 22 KJ/cm2. Subsequent studies by the same authors displayed improvement of the acne and seborrhoea conditions, as well as a reduction in the concentration of porphyrins in the lesions, using blue light (high pressure bulb type) after 10 irradiations with an accumulated light dose of 325 J/cm [49].

Shalita et al [50] cultivated *P. acnes* removed from lesions in the patients' frontal region, before and after six fortnightly treatments with high intensity, narrow-band, blue light without UV. *P. acnes* cultures were accomplished before the therapy, and after the 2nd, 4th and 6th treatments, both in areas that received the light and in the not irradiated symmetrical areas. Around 60% of the patients showed a significant reduction

(90%) in *P. acnes* levels. The four patients who did not show significant changes were those who presented low base levels of *P. acnes*.

Sigurdsson et al 40 showed a significant improvement in inflammatory acne lesions with green light (22%) and violet light (35%), yet with less evident improvement in the comedones, showing that visible light alone can be effective for the treatment of acne, especially the inflammatory type.

Using a high intensity source of light (407-420 nm at the flow index of 90 mW/cm2), Kawada et al [51] showed an outstanding effect that lasted at least 1 month in light to moderate cases of acne.

Arruda et al [52] compared blue light with 5% benzoyl peroxide topical therapy in the treatment of inflammatory acne grades II and III. They concluded that the blue light treatment was as effective as the 5% benzoyl peroxide, but involved fewer adverse effects.

These studies suggest that phototherapy with blue light, when used on patients with light to moderate acne, represents an effective, lasting therapeutic option that is in general well tolerated and lacks significant side effects.

COMBINATION OF BLUE AND RED LIGHT

As previously described, the irradiation of *P. acnes* with blue light (415 nm) results in the photodynamic stimulation of the porphyrins stocked in the bacterium, leading to the

formation of singlet O2 and its consequent death [53]. Moreover, it has been observed that when associated with UVA, blue light causes changes in the intracellular pH, altering the transmembrane flow of ions, which damages the bacteria 46. In spite of these and other studies showing its great potential, blue light's effectiveness as a treatment is limited by its low penetration in the skin.

Red light, although less effective in the photoactivation of porphyrins, penetrates more deeply in the tissues and has anti-inflammatory properties that influence the liberation of cytokines from the macrophages and other cells [54]. Macrophages exposed to wavelengths of around 660 nm liberate cytokines, which stimulates the proliferation of fibroblasts and the production of growth factors, influencing the wound's healing and repair process [55]. Red light emitting lasers can also affect the cellular membrane's permeability to calcium ions [56]. Regarding its anti-inflammatory action [57] and its deep tissue penetration capacity, the combined use of blue and red lights is a promising option in the treatment of acne. Papageogiou et al [58] evaluated the use of blue light (peak of 415 nm) and a blend of blue and red lights (peaks of 415 nm and 666 nm) in a randomized, controlled and double-blind study of patients with light to moderate acne. The 107 patients were divided into four treatment groups: blue and red light phototherapy, blue light, cold white light, and cream with 5%

benzoyl peroxide. The patients used portable light sources and 15-minute irradiations were implemented daily. Evaluations were made every four weeks. After 12 weeks of follow up, improvements to 76% of the inflammatory lesions were found when using the blue/red phototherapy – a significantly superior result compared to the other groups. There was a 58% improvement to comedones using the combined therapy – although these differences did not reach significant levels, they were also superior to other groups. The authors concluded that the combined use of blue and red lights in phototherapy, probably due to their antibiotic and anti-inflammatory synergic actions respectively, is an effective means of treating acne vulgaris of light to moderate severity, without significant side effects.

CONCLUSIONS

Acne vulgaris is one of the most common pathologies found in daily clinical practice. Patients with acne vulgaris present a constant challenge to the extent that the condition must be considered from a social-psychological perspective, in addition to the clinical. The control of acne in many cases may mean the prevention of depression, social phobias, and even suicide.

Although we have a vast pharmaceutical arsenal for the treatment of acne, and drugs are still the main therapeutic option with very satisfactory results in general, there are countless serious side effects associated with some medicines in addition to the growing bacterial resistance of *P. acnes*, as discussed in the studies cited. The efficacy of the treatment still depends on the patient's level of motivation and persistence in the use of the medications.

The numerous studies that led to a better understanding of the physiopathology and photobiology of acne, combined with recent advances in light-based technological devices, allowed the emergence of new therapeutic modalities, in particular phototherapy.

These studies demonstrate that phototherapy improves cases of acne – especially inflammatory ones – of light to moderate severity, and that this improvement may persist for several months. In general, the side effects are few and well tolerated.

The combined use of the blue and red lights behaves in a synergic way due to their respective antibiotic and anti-inflammatory properties. Preliminary studies indicate that this combination is a promising and safe option in the treatment of acne.

ALA-PDT also produces good results in several studies due to its capacity to disable the sebaceous glands and destroy *P. acnes*, however some side effects are described.

Phototherapy, still in the early stages of clinical use, demands new studies with larger samplings and longer follow ups – in addition to comparative studies with already established therapies – so that it can be recognized and used in daily practice.●

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