Folia Medica Indonesiana Vol. 53 No. 4 December 2017 : 272-275

EFFECTS OF BLUE LIGHT EMITTING DIODE (LED) AND DOXYCYCLINE TO SEBACEOUS GLAND IN ACNE VULGARIS

M Yulianto Listiawan, Cita Rosita Sigit Prakoeswa, Dhyah Aksarani Handamari, Regitta Indira
Departement of Dermatovenereology, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo Hospital, Surabaya

ABSTRAK

Akne vulgaris (AV) merupakan peradangan pada unit pilosebasea terutama pada dewasa muda. Patofisiologinya adalah peningkatan produksi sebum, keratinisasi folikel pilosebaseus yang abnormal, dan inflamasi akibat respons imun terhadap Propionibacterium acnes. Kombinasi terapi antara antibiotik oral (doksisiklin) dengan terapi fisik (blue light) terutama pada akne derajat sedang berat merupakan pilihan terapi untuk menurunkan resistensi antibiotik. Doksisiklin merupakan antibiotik pilihan yang sering digunakan. Efek fotosensitifnya dapat meningkatkan penetrasi sinar biru oleh kelenjar sebaseus. Terdapat penurunan total sebum dan perbaikan klinis terapi kombinasi sinar biru dan doksisiklin pada tujuh pasien. Terapi kombinasi tersebut terbukti meningkatkan efek terapeutiknya, namun diperlukan lebih banyak uji klinis untuk membuktikan efektifitas sinar biru dengan doksisiklin dibandingkan tanpa sinar biru. ***(FMI 2017;53:272-275)***

Kata kunci*: Akne vulgaris; doksisiklin; sinar biru*

ABSTRACT

Acne vulgaris (AV) is an inflammation of pilosebaceous unit especially in young adult. The pathophysiology is the elevation of sebum production, keratinization of abnormal pilocebaseous follicles, and inflammation caused by immune response to Propionibacterium acnes. Therapy combination of oral antibiotics (doxycycline) and physical therapy (blue light) in moderate-severe acne is one option to reduce antibiotic resistance. Doxycycline is a commonly antibiotic used. The effects of photosensitive can increase the penetration of blue light by sebaceous glands. There was a total decrease in sebum and clinical improvement of combination therapy of blue light and doxycycline in seven patients. The combination therapy has been shown to improve its therapeutic effect, but more clinical trials are needed to prove the effectiveness of blue light with doxycycline than without blue light. ***(FMI 2017;53:272-275)***

Keywords*: Acne vulgaris; doxycycline; blue light*

Correspondence: M. Yulianto Listiawan, Departement of Dermatovenerology, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo Hospital, Surabaya. Email: yuliantowawan@yahoo.com

INTRODUCTION

Acne vulgaris (AV) is a self-limited disorder of pilosebaceous unit that is associated with oil gland and is seen primarily in adolescents (Zaenglein 2012). The clinical features of AV include non-inflammatory lesions (open and closed comedones), inflammatory lesions (papules and pustules), nodules or cysts, and scar . The distribution of acne depends on the highest density of pilosebaceous units (face, neck, upper chest, shoulders, and back).

A degree of acne affects nearly all people between the ages of 15-17 years. In 15–20% of young people, acne is moderate to severe. Acne can occur in prepubertal children, but this is usually noninflammatory in nature as children have not produced sebum yet, which provides the correct environment to host P. acnes (Bhate & Williams 2012).

The pathogenesis of acne is multifaceted, but four basic steps have been identified. These key elements are follicular epidermal hyperproliferation, excess sebum production, inflammation, and the presence and activity of *Propionibacterium acnes* (*P. acnes*). These four factors are illustrated in Fig. 1. The role of P. acnes in pathogenesis is unclear, while antibiotics have a direct antimicrobial as well as an anti-inflammatory effect. Moderate-to-severe acne affects around 20% of young people and severity correlates with pubertal maturity (Bhate & Williams 2012).

As already mentioned, increased sebum is a major factor associated with acne pathogenesis. Grossly, increased sebum provides an anaerobic, lipid-rich follicle in which *P. acnes* can proliferate. However, the specifics of how sebum functions have not yet been clarified. One suggestion is that reduced water loss from the facial surface, which protects the skin surface from certain bacteria or fungi and delivers vitamin E, might be involved (Youn 2010). Previous studies have found

the positive correlation between the sebum secretion and acne. However, the population samples of previous studies were small or the method to evaluate the acne severity was a subjective grading system. Moreover, the sebum measurement methods were not standardized (Chol et al 2011).

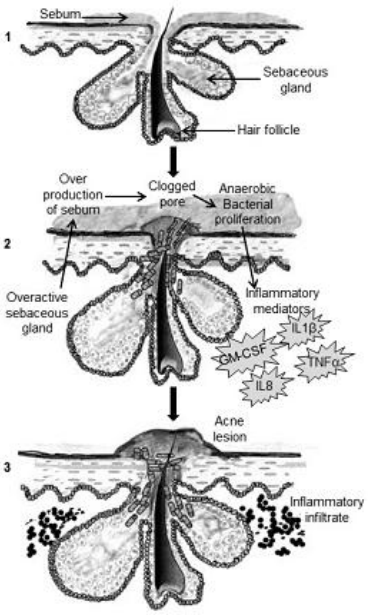

Fig. 1. Pathogenic factors contributing to the development of acne: (1) The normal pilosebaceous unit. (2) The clogging of the pore is aggravated by hyperkeratinization and excess sebum production whilst anaerobic bacteria (mainly *P. acnes*) proliferate and inflammatory mediators are released. (3) Inflammatory infiltrates cause the development of increasing degrees of severity in inflammatory acne forms (Fox et al 2016).

Understanding the underlying basis for acne and the mechanisms of action of the multitude of therapeutic options in treating acne will assure better therapeutic results. Although current acne guidelines discourage the use of antibiotics as prolonged monotherapy, about 5 million prescriptions for oral antibiotics are written each year for the treatment of acne. Antibiotics demonstrate anti-inflammatory and antimicrobial effects and work on two levels: to decrease the presence of P. acnes – a resident of the normal microflora found in abnormally high numbers in the sebaceous follicles of patients with acne and a primary factor in the development of inflammatory acne and to inhibit the production of *P. acnes* associated inflammatory mediators. The last 30 years have witnessed an alarming increase in resistance to antibiotics commonly employed to treat acne. Antibiotic resistance in acne represents a significant international public health concern because resistance can occur in more pathogenic bacteria than *P. acnes*, and an increase in pathogenic *P. acnes* has been reported. Antibiotic resistance is one of the health problem in Indonesia, the one of the reason is using combination of antibiotic, so that clinician should prevent resistance to any selected combination antibiotic therapy. *P. acnes* resistance to antibiotics increased from 20% in 1979 to 67% in 1996. Current treatment guidelines offer strategies to limit the potential for resistance while achieving optimal outcome in the management of inflammatory and non-inflammatory acne (Humphrey 2012, Rimadhani & Rahmadewi 2015).

Alternative treatments for treating acne, such as lasers and light therapy, are gaining importance because of the emergence of antibiotic-resistant *P. acnes*, the side effects of antibiotics, and because some patients are intolerant or resistant to oral retinoids. All the above-mentioned studies provide attractive alternative treatment options for the clinician to choose from when treating acne patients. High-intensity, narrow-band, and blue light phototherapy is promising new treatment for acne. It is believed that blue light, by killing or altering the function of *P. acnes*, decreases the severity of acne, especially inflammatory acne. A study conducted by Shnitkind et al (2006) showed that blue light has anti-inflammatory effects on keratinocytes by decreasing the cytokine-induced production of interleukin-1 alpha and intercellular adhesion molecule-1. Its side effect is still mild and includes temporary pigment changes, swelling of treated areas, and dryness (Ammad et al 2008). The goal of this study was to evaluate the efficacy of blue light-emitting diode (LED) technology with oral doxycycline in treating inflammatory acne.

MATERIALS AND METHODS

This perspective study was performed in accordance with the guidelines of the 2015 Indonesian Acne Expert Meeting. Seven female patients (mean age: 22.3 years; range: 20–26 years; Fitzpatrick skin type: III-IV), who were treated using oral doxycycline and blue light for moderate AV with inflammatory lesions, were reviewed in this study. Patients with active and multiple inflammatory lesions at the time of blue light treatment were enrolled. Subjects were excluded from this study if they had recently received systemic retinoid; light or laser therapy within 6 months; or were treated with systemic and topical antibiotics, intralesional corticosteroid injection, incision and drainage, and pregnancy. Patients were treated with oral 100 mg doxycycline two times daily for 4 weeks and high-intensity pure blue light using a Acne Photo Light (APL) type B class I from MEDRO Medical Div. Co., Ltd (Seoul, Korea), receiving one treatment per week of 10 minutes (415

nm, 40 J/cm2) for 4 weeks. Clinical assessment was performed at baseline, week 3, week 5 and week 8. Patients' therapeutic response was measured using Janus skin analyzer. Patients' tolerance, side effects and observations were monitored and documented throughout the study period.

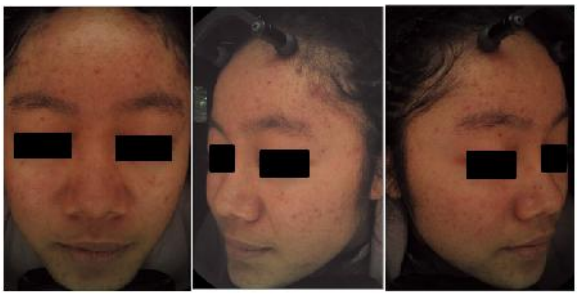

Fig. 2. Before treatment.

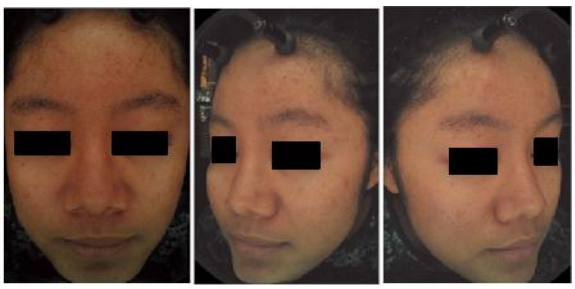

Fig. 3. After the therapy of 4 times blue light and 2 times 100 mg doxycycline daily for 4 weeks. There is reduction of total sebum.

Seven patients were completed in 4 weeks of treatment. No adverse event was reported during the treatment. All of the patients experienced complete clearing in 8 weeks. A significant number of patients reported a decrease in skin oiliness, which leads to decrease number of papules and pustules. Examination with Janus skin analyzer also showed a reduction in the total sebum.

DISCUSSION

The pathophysiology of acne is complex and multifactorial, including the role of hyperseborrhea and pilosebaceous colonization with *P. acnes*. A reduction of those two factors is also associated with improvement of acne severity in patients. *P. acnes* is responsible for the production of endogenous porphyrins, mainly coproporphyrin III and protoporphyrin IX that have a spectrum of maximal absorption in the range of 400 to 415 nm. The excitation of endogenous porphyrins by high-intensity specific light sources, such as blue LED, has been shown to decrease bacterial count in acne prone skin (Brownell et al 2016).

High-intensity and narrow-band blue light phototherapy has been approved by the US Food and Drug Administration for treating acne. It is being used to treat inflammatory acne, which has not responded to other acne therapies. Generally, eight sessions are given over a period of 4 weeks, and each session lasts approximately about 15 min. Side effects reported to date have been mild and include temporary pigmentary changes, dryness, and rarely some swelling of treated areas. Many patients but not all respond very well to blue light therapy (Webster 2010).

Sebum is the central problem in acne. Without it, *P. acnes* cannot proliferate, and acne will not exist. The most effective drug for the disease, isotretinoin, exerts most of its effects on sebum secretion. A light-based treatment that targets sebum production would have the potential to cure acne. Most likely, it could not be done without sebaceous glands. The function of sebum is unknown. It may serve to inhibit invading bacteria, such as dermatophytes and streptococci, but children do well with no sebum, and adults have little to no sebaceous activity on the extremities, with no ill effects. The challenge in a therapeutic attack on the sebaceous gland is its distance from the skin surface. Between the gland and the surface, there is up to 3 mm of tissue that can absorb light. It is suspected that there were developments of a molecule that homes to the sebaceous gland then can be activated by an otherwise innocuous wavelength of light (Dai et al 2012, Webster 2010).

Blue light has been shown to have an antiproliferative effect on cell lines, which can be used in the treatment of acne. An in vitro study found that irradiation of human sebocytes with 415-nm light reduced their proliferation, and this effect was dose dependent. In reducing the number of sebocytes, the amount of sebum available to *P. acnes* is reduced, thus decreasing the ability of *P. acnes* to induce inflammation. Blue light is also known to have a direct antimicrobial effect on *P. acnes*. *P. acnes* naturally produces photosensitizing porphyrins. Bacteria exposed to high doses of 407 to 420 nm light showed decreased culture viability. Exposed cells had an increased coproporphyrin product-ion, indicating that photoinactivation of these cells may be mediated by this endogenous porphyrin production. Blue light is believed to excite these endogenous porphyrins, leading to the production of cytotoxic reactive oxygen species that cause the death of the bacterium (Brownell et al 2016).

In an in vitro study conducted by Kawada et al (2002), five *P. acnes* strains isolated from randomly-selected

acne patients were used to assess the antimicrobial efficacy of blue light (407–420 nm). Bacterial suspensions were exposed to blue light for 60 min at a distance of 25 cm with an irradiance of 90 mW/cm^2 (i.e., total radiant exposure 324 J/cm^2 at the lamp aperture). P. acnes viability was decreased by 15.7% and 24.4%, respectively, immediately and at 60 min after the irradiation.

In another study, Ashkenazi et al (2003) used an intense blue light lamp (407–420 nm) to inacti-vate *P. acnes*. Cultures in the test tubes were subjected to illumination by placing the test tubes horizontally in order to obtain maximal exposure to the blue light. Some cultures were illuminated again after 24 h and some were even illuminated three times, after an additi-onal 24 h. The lamp was located 10 cm above the horizontal test tube and produced 20 mW/cm2 homo-geneous illumination at the culture tube surface. Two ventilators are also located near the lamp on both sides in order to prevent any heating of the illuminated sam-ples.

The viability of 24 hours cultures grown anae-robically in liquid medium was reduced by less than 2-log10units (99%) when illuminated once with a light dose of 75 J/cm^2. Better photo inactivation effects were obtained when cultures were illuminated twice or three times consecutively with a light dose of 75 J/cm^2 and an interval of 24 h between illuminations. The viability of the culture under these conditions decreased by 4-log10 units (99.99%) after two illuminations and by 5-log10 units (99.999%) after three illuminations. X-ray micro-analysis and transmission electron microscopy revealed structural damages to membranes in the illuminated *P. acnes* (Dai et al 2012).

CONCLUSION

Blue LED therapy, which offers a non-invasive alternative treatment of acne, should now be seen as a credible treatment modality with growing interest for inflammatory acne treatments. Combination treatment of blue light and oral doxycycline, as a photosensitizer, could elevate the penetration of blue light into the sebaceous gland thus accelerating the treatment of acne and is expected to decrease the resistance rate. Further research is needed to prove it.

REFERENCES

Ammad S, Gonzales M, Edwards C, Finlay AY, Mills C (2008). An assessment of the efficacy of blue light phototherapy in the treatment of *Acne vulgaris.* Journal of Cosmetic Dermatol 7, 180–8

Ashkenazi H, Malik Z, Harth Y, Nitzan Y. Eradication of *Propionibacterium acnes* by its endogenic porphyrins after illumination with high intensity blue light. FEMS Immunol Med Microbiol 35, 17-24

Bhate K, Williams HC (2012). Epidemiology of acne vulgaris. British Association of Dermatologists 168, 474–85.

Brownell J, Wang S, Tsoukas MM (2016). Phototherapy in cosmetic dermatology. Clinics in Dermatol 34, 623–7

Chol CW, Chol JW, Park KC, Youn SW (2011). Facial sebum affects the development of acne, especially the distribution of inflammatory acne. JEADV, 1-6

Dai T, Gupta A, Murray CK, Vrahas MS, Tegos GP, Hamblin MR (2012). Blue light for infectious diseases: *Propionibacterium acnes*, *Helicobacter pylori*, and beyond?. Drug Resistance Updates 15, 223–36

Fox L, Csongradi C, Aucamp, Plessis, Gerber M (2016). Treatment Modalities for Acne. Molecules 21, 1063-83

Humphrey S (2012). Antibiotic resistance in acne treatment. Skin therapy Letter 17, 1-3

Kawada A, Aragane Y, Kameyama H, Sangen Y, Tezuka T (2002). Acne phototherapy with a high-intensity, enhanced, narrow-band, blue light source: an open study and in vitro investigation. J Dermatol Sci 30, 129-35

Rimadhani M, Rahmadewi (2015). Antibiotik oral pada pasien Akne vulgaris: penelitian retrospektif. Berkala Ilmu Kesehatan Kulit dan Kelamin 27, 84-9

Shnitkind E, Yaping E, Geen S, Shalita AR, Lee WL (2006). Anti-inflammatory properties of narrow-band blue light, J Drugs Dermatol 5, 605-10

Webster GF (2010). Light and laser therapy for acne: sham or science? facts and controversies. Clinics in Dermatol 28, 31–3

Youn SW (2009). The role of facial sebum secretion in acne pathogenesis:facts and controversies. J clin dermatol 28, 8-11

Zaenglein AL, Graber EM, Thiboutot DM (2012) Acne vulgaris and acneiform eruptions. In: Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K, editors. Fitzpatrick's Dermatology in general medicine. 8th ed, New York, McGraw-Hill Inc, p 897-917