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State of the art of blue light effects on hidradenitis suppurativa: a concise systematic review

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Abstract

Introduction: In the setting of inflammatory diseases, hidradenitis suppurativa (HS), or acne inversa, is an immune-mediated skin disease with a prevalence of 0.1-1% and characterized by nodules and abscesses in the armpits, groin, and inframammary areas, which may evolve for fistulas and scars. Still, an update is needed on the recent understanding of the pathogenesis of HS, including the central role of inflammatory cytokines and other contributing factors such as genetics, hormones, and pathogenic microorganisms. As an innovative approach, antimicrobial blue light in the 400-470 nm spectrum has demonstrated its intrinsic antimicrobial properties resulting from the presence of endogenous photosensitizing chromophores in pathogenic microorganisms. **Objective:** To carry out a narrative and systematic review of the literature to explore the main clinical and experimental results of the use of photobiomodulation with blue light for the treatment of hidradenitis suppurativa by antibacterial action. **Methods:** The present study followed a model of narrative and systematic review, according to PRISMA rules, to gather the main information about the efficiency and safety of blue light in the treatment of HS. The research was carried out from January 2018 to May 2019 and developed based on Google Scholar, Scopus, PubMed, Scielo, and Cochrane Library. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results:** Microorganisms are less able to develop resistance to antimicrobial blue light than to traditional antibiotics, due to the multi-targeting characteristics of antimicrobial blue light. Furthermore, it is well accepted that antimicrobial blue light is much less harmful to host cells than UV irradiation. Clinical studies have presented scientific evidence of treatment for HS with light-based therapy, showing efficacy and safety through articles published in quality journals in scientific evidence. A meta-analysis published in 2019, based on the quality of the evidence, showed that the most recommended treatments for HS include adalimumab and laser (blue light) therapy. For intense pulsed light with blue light, two RCTs reported improvements in HS-LASI scores and the Dermatology Quality of Life Index. **Conclusion:** The use of blue light for dermal treatments, particularly for HS, is finding an increasing role in dermatology. However, more robust and consistent studies are still needed to better demonstrate the antibacterial effects of blue light on HS.

Keywords: Hidradenitis suppurativa. Blue light. Photobiomodulation. Antibacterial action. Inflammatory processes.

Introduction

In the setting of inflammatory diseases, hidradenitis suppurativa (HS), or acne inversa, is an immune-mediated skin disease with a prevalence of 0.1-1% and characterized by nodules and abscesses in the armpits, groin, and inframammary areas, which can progress to fistulas. and scars. It typically begins in early adulthood, with inflamed skin nodules, abscesses, and pus discharge tunnels that develop in axillary, inguinal, gluteal, and perianal body sites. HS is more common in women aged between 18 and 40 years [1,2].

In this context, HS comorbidities include metabolic and cardiovascular disorders, reducing the quality of life. As etiological factors, genetic predisposition, smoking, obesity, and hormonal factors stand out. The skin

changes appear to start around the hair follicles and involve the activation of cells of the innate and adaptive immune system, with central roles for pro-inflammatory cytokines such as tumor necrosis factor, IL-1β, and IL-17. This chronic immune response causes severe pain, pus secretion, irreversible tissue destruction, and scarring. Common therapeutic options for HS include antibiotic therapy, tumor necrosis factor neutralization, and surgical intervention associated with lifestyle modification [3].

Also, although the mechanism of HS has not been fully elucidated, lesion formation is believed to occur around follicular hyperkeratosis within the pilosebaceous-apocrine unit. Still, an update is needed on the recent understanding of the pathogenesis of HS, including the central role of inflammatory cytokines and other contributing factors such as genetics, hormones, and pathogenic microorganisms [4].

In this sense, treatment options range from short or long courses of antibiotics, anti-inflammatories, biologics, and surgery. Other suggested treatments consider the use of laser devices, mainly microsurgical lasers (such as CO2 and intense pulsed laser) and photodynamic therapy. It was highlight the potential use of photobiomodulation (PBM), already used for the treatment of other skin diseases, such as acne, hypertrophic scars, wrinkles, and burns, as a potential new therapy for HS. PBM has been reported to have beneficial effects in promoting wound healing, angiogenesis, vasodilation, and alleviating pain and inflammation, as recently demonstrated in an in vitro model that mimics HS disease. Furthermore, PBM, specifically defined at the blue wavelength, was recently reported to exert antibacterial activity [5].

As an innovative approach, antimicrobial blue light in the 400-470 nm spectrum has demonstrated its intrinsic antimicrobial properties resulting from the presence of endogenous photosensitizing chromophores in pathogenic microorganisms and its promise as a bactericide of antibiotic resistance [6].

In this regard, microorganisms are predicted to be less capable of developing resistance to antimicrobial blue light than to traditional antibiotics, due to the multi-targeting characteristics of antimicrobial blue light [7-9]. Furthermore, it is well accepted that antimicrobial blue light is much less harmful to host cells than UV irradiation [10,11].

Therefore, the present study aimed to carry out a narrative and systematic review of the literature, to explore the main clinical and experimental results of the use of photobiomodulation with blue light for the treatment of hidradenitis suppurativa by antibacterial action.

Methods

Study Design

The present study followed a narrative and systematic review model, to gather the main information on the efficiency and safety of blue light in the treatment of hidradenitis suppurativa. The rules of the Systematic Review-PRISMA Platform (Transparent reporting of systematic reviews and meta-analysis-HTTP://www.prisma-statement.org/) were followed

Data Sources and Research Strategy

The search strategies for this review were based on the descriptors: "*Hidradenitis suppurativa. Blue light. Photobiomodulation. Antibacterial action. Inflammatory processes*". The research was carried out from January 2021 to April 2022 and was developed based on Google Scholar, Scopus, PubMed, Scielo, and Cochrane Library. In addition, a combination of the keywords with the Booleans "OR", "AND" and the "NOT" operator were used to target scientific articles of interest.

Study Quality and Risk of Bias

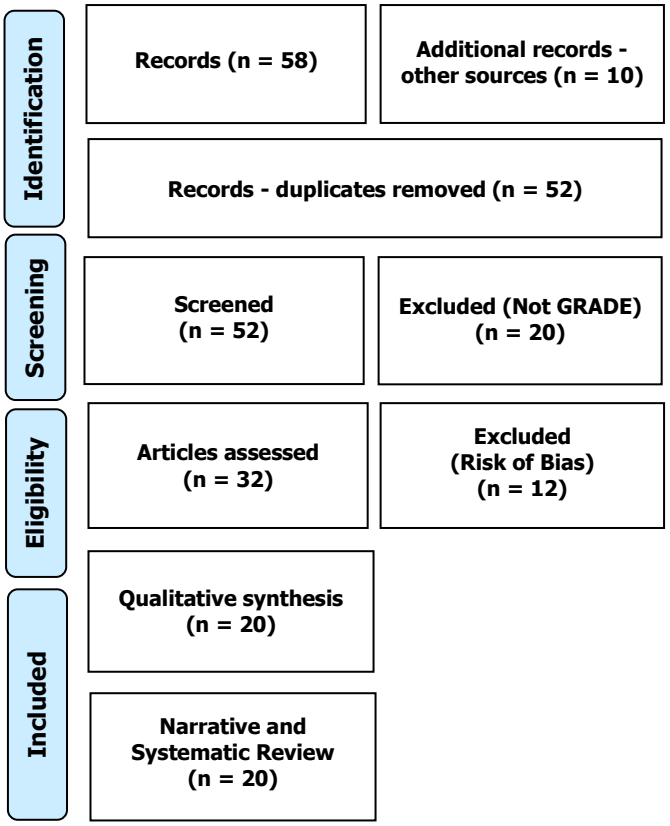
The quality of the studies was based on the GRADE instrument, with randomized controlled clinical trials, prospective controlled clinical trials, and systematic review and meta-analysis studies listed as the studies with the highest scientific evidence. The risk of bias was analyzed according to the Cochrane instrument.

Results

A total 68 studies were analyzed, and only 20 medium and high-quality studies were selected, according to GRADE standards, and with risks of bias that do not compromise scientific development, based on the Cochrane instrument (**Figure 1**).

As a corollary of the exploration of the 20 studies, some studies have demonstrated the safety and efficacy of the application of blue light with antibacterial action. As an example, *Propionibacterium acnes* (P. acnes) is an opportunistic infection of the human skin that causes acne vulgaris. Photodynamic inactivation is a non-antibiotic therapy for microbial eradication. In this regard, in one study, visible blue light (BL) (BL, λmax = 462 nm) was used to increase the antimicrobial activities of curcumin, a natural phenolic compound. Individual exposure to curcumin or BL irradiation does not generate cytotoxicity in P. acnes. The viability of *P. acnes* significantly decreased by 0.09 J/cm2 BL with 1.52 μM curcumin. Furthermore, low-dose blue light irradiation triggers a series of cytotoxic actions of curcumin in *P. acnes* [12].

Figure 1. Selection of studies.



In an experimental study in dogs, blue light inhibited the growth of *S. pseudintermedius*, the effect increased significantly with the addition of 5-aminolevulinic acid (ALA) as a photosensitizer and with increasing light doses. Live/dead staining confirmed that PDT reduced bacterial viability and exerted an antibacterial effect. Blue light has a strong antibacterial effect on *S. pseudintermedius* in a light dose-dependent manner. ALA alone did not exhibit bactericidal action, but its combination with blue light increased the effect of PDT compared to blue light alone [13].

In this context, a systematic review study that analyzed 248 patients involved in clinical trials has presented scientific evidence of treatment for HS with light-based therapy, showing efficacy and safety through articles published in quality journals in scientific evidence [14]. In this context, several medical treatments are available for HS, such as antibiotics, retinoids, antiandrogens, immunosuppressive and anti-inflammatory agents, and radiotherapy for early lesions. However, a meta-analysis published in 2019, based on the quality of the evidence, showed that the most recommended treatments for HS include adalimumab and laser (blue light) therapy [15].

Furthermore, the formation of antibiotic-resistant bacterial biofilms was found to be a common finding in HS lesions. A retrospective study reported the results of treating HS with photodynamic therapy using intralesional methylene blue and a 635 nm light-emitting diode lamp in 7 patients. Two patients received one session, while 5 patients received two sessions. At one-month follow-up, a good response was achieved in 6 patients. After 6 months, 5 patients (71%) maintained disease remission in the treated area [16].

Also, BL photodynamic therapy using topical 20% ALA (BL-ALA) is being used to treat a variety of dermatological skin conditions, primarily HS. One study evaluated the effectiveness of BL-ALA in treating recalcitrant cases of HS. Four patients, who did not respond to standard HS therapy, underwent short-contact BL-ALA therapy. Intervals of one to two weeks were used between therapies for 3-4 treatments in total and follow-up was 3 months after the last treatment. All four patients tolerated the therapies well. Clinical improvements of 75-100% were observed in patients. No adverse effects were observed during the treatments. The treatments were painless. Therefore, HS is a chronic disease that is difficult to treat for most dermatologists. The use of BL-ALA is finding an increasing role in dermatology [17].

Another study investigated the efficacy and safety of ALA for the treatment of HS using both blue light and intense pulsed light (IPL) sources for photoactivation. Twelve subjects with active HS enrolled to undergo the study once a week for four weeks with follow-up visits 4, 8, and 12 or more weeks later. Nine subjects completed the study during the week 8 follow-up visit. Lesions were counted at each treatment visit at week 4, week 8, and the final week. The median injury count was 11.25 at baseline, 6.5 at 4 weeks (50.8% reduction), and 7.5 at 8 weeks (29.9% reduction). The mean global severity scores were 2.2 at baseline, 1.5 at 4 weeks, and 1.8 at 8 weeks. The mean DLQI scores were 17.3 at baseline, 13.1 at 4 weeks (27.2% improvement), 14.00 at 8 weeks (19.3% improvement), and 14.0 (19.3% improvement). 19.3%) in the final week (16-62 weeks). Three subjects (25%) had complete elimination and no active lesions 4 weeks after the final treatment. The treatments were more tolerable for subjects treated with blue light than with IPL [18].

Besides, a randomized study evaluated the efficacy and safety of methylene blue as a photosensitizer delivered as a niosomal gel for the treatment of HS using pulsed light. Eleven patients with HS were included. One side of each patient's body was treated with methylene blue and niosomal gel (MBN) and the other side was treated with methylene blue and free (MBF) gel. Affected sites were irradiated using pulsed light with a 630 nm filter. Patients were followed at 1, 3, and 6 months after treatment. Drug release from the MBF gel was significantly higher ($p>0.05$) than from the MBN gel. Lesions showed a reduction of 77.3% and 44.1% on the MBN and MBF sides, respectively. A significant

reduction in the Lesion, Area and Severity Index of Hidradenitis Suppurativa (HS-LASI) after treatment was induced in both groups, without pain, erythema, or hyperpigmentation. Thus, the combination of methylene blue as an activated photosensitizer with 630 nm pulsed light as a light source is a successful antibacterial photobiomodulation for HS. Delivery of MB in niosomes was more effective for drug penetration into the dermis compared to delivery by gel of MBF. The 630 nm filter was not only a source of MB activation but also a means of hair follicle destruction [19].

Finally, an important systematic review and meta-analysis study analyzed the effectiveness of non-ablative light-based devices in the treatment of HS. This study explored 5 Randomized Controlled Trials (RCT) and 11 case reports/series (n = 211 patients). For Nd: YAG laser, a meta-analysis of 3 randomized controlled trials reported improvement in modified HS lesion area and severity index (HS-LASI) when compared to control subjects. In addition, three case reports/series reported HS-LASI, Physician Global Assessment (PGA) scores, and improvements in the number of lesions in treated patients. For intense pulsed light with blue light, two RCTs reported improvements in HS-LASI scores and the Dermatology Quality of Life Index [20].

Conclusion

The use of blue light for dermal treatments, particularly for hidradenitis suppurativa, is finding an increasing role in dermatology. However, more robust and consistent studies are still needed to better demonstrate the antibacterial effects of blue light on hidradenitis suppurativa.

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No additional data are available.

Conflict of interest
The authors declare no conflict of interest.

Similarity check
It was applied by Ithenticate@.

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