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ORIGINAL ARTICLE

The Interventions to Minimize Pain During Photodynamic Therapy With 5-Aminolevulinic Acid for the Treatment of Cutaneous Diseases

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ABSTRACT

Photosensitization with 5-aminolevulinic acid (ALA) combined with photodynamic therapy (PDT) is approved in the United States for the treatment of actinic keratosis (AK) and is used off-label for other indications including acne treatment and photo rejuvenation. However, pain, particularly during the initial illumination period, limits the utility of this highly efficacious therapy. Although modifications to conventional ALA-PDT protocols that improve tolerability without diminishing efficacy have been identified, few have been evaluated in randomized, controlled trials, and the number of variables involved in ALA incubation (eg, duration, occlusion, ALA formulation, and strength) and PDT illumination (eg, light source, fluence rate, irradiance, and duration) confounds standardization.

Perhaps the most promising modifications to date involve continuous activation of low levels of protoporphyrin IX, the photoactive metabolite of ALA, as well as using shorter incubation times (with or without prolongation of illumination), lower irradiance, and daylight or combined (daylight and conventional) PDT. However, reimbursement of PDT with alternative light sources in the US is hampered by the US Food and Drug Administration (FDA) labeling, which specifies the blue or red light devices approved for use with corresponding marketed ALA 20% solution and 10% gel, respectively. This review summarizes the existing evidence with respect to pain control in patients undergoing ALA-PDT, recommendations from clinical experience, and goals for future research.

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INTRODUCTION

Actinic keratosis (AK) is a common skin lesion that classically presents as a rough, scaly papule on an erythematous base; AKs typically arise in areas chronically exposed to ultraviolet light and may progress to squamous cell carcinoma if untreated.[1] Photodynamic therapy (PDT) is conditionally recommended for the treatment of AK by the American Academy of Dermatology (AAD).[1]

Conventional PDT involves the application of a photosensitizing compound (usually 5-aminolevulinic acid [ALA] or methyl-5-aminolevulinate [MAL]) to the affected skin and incubation for 3 or more hours. During incubation, ALA and MAL are metabolized to protoporphyrin IX (PpIX), a photoactive compound that can be activated by light in the presence of oxygen to form reactive oxygen species that damage cellular components and cause cell death.[2-4] Although abundant literature supports the use of MAL-PDT for the treatment of AKs,1 MAL is not FDA approved or commercially available in the US.

In the United States, ALA 20% solution is approved by the Food and Drug Administration (FDA) in combination with blue light illumination (BLU-U®) for lesion-directed treatment of minimally to moderately thick AKs of the face, scalp, and upper extremities;[2] whereas ALA 10% gel is approved in combination with BF-RhodoLED® red light for lesion-directed and field-directed treatment of AKs of mild-to-moderate severity on the face and scalp.[3] ALA is also used – off-label in the US – for the treatment of nonmelanoma skin cancers (NMSC; ie, squamous cell carcinoma in situ/Bowen's disease and superficial or nodular basal cell carcinoma [BCC]) and acne vulgaris.[4]

Pain during treatment is a drawback of ALA-PDT. Local skin reactions, including stinging/burning and erythema, are common during and shortly after illumination and can be severe.[2,3] Patients may have difficulty tolerating multiple treatments or even a full treatment session.[5] Furthermore, adjunctive measures to improve efficacy or decrease required incubation time may increase pain; these include skin preparation by curettage[4,6] or microneedling[7] and incubation with occlusion.[8] Despite these considerations, the 2021 AAD guidelines devote little attention to pain mitigation during ALA-PDT.[1] This review summarizes the available medical literature on attempts to reduce pain associated with ALA-PDT, focusing on

prospective, randomized comparisons evaluating modifications of conventional protocols and their impact on efficacy and pain of ALA-PDT in AK (Table 1), as well as providing the author's clinical recommendations.

Adjunctive Measures to Reduce Pain During Illumination

Efficacy of topical anesthetics for pain management during PDT appears limited. In patients undergoing PDT for AK or other skin conditions, no significant pain reductions were observed with the use of morphine gel[9] or a lidocaine 2.5%-prilocaine 2.5% mixture[10] vs placebo. Standard fans and misting with water may also be used to alleviate pain during PDT.[4] Patients receiving ALA-PDT for AK on the face or scalp reported significant reductions in pain scores with cold air analgesia compared with a standard fan, with no effect on the rate of complete AK clearance (Table 1).[11]

Brooke et al reported that histamine mediates the immediate urticarial response to ALA-PDT (ie, wheal and flare), but not the delayed phototoxic reaction, in healthy volunteers.[12] However, in a randomized trial in patients undergoing ALA-PDT, the oral antihistamine cetirizine did not decrease signs of inflammation and discomfort (Table 1).[13]

Factors Influencing Pain During ALA-PDT

Incubation Time

The FDA labeling for ALA 20% solution and ALA 10% gel recommends incubation periods of 14 to 18 hours and 3 hours, respectively, for PDT of AK on the scalp or face.[2,3] However, PpIX accumulation becomes statistically higher vs baseline after 2 hours in almost all AK lesions.[14] The AAD guidelines for treatment of AK conditionally recommend 1- to 4-hour incubation when using ALA with red light PDT but do not specify incubation time before blue light PDT.[1] Reduction in ALA incubation time (with or without adjustment to illumination time) to attenuate PpIX accumulation in the skin has been investigated as a way to reduce pain during illumination. The irony in the use of PDT today is that 14-18 hour incubation is tantamount to a daylight PDT regimen, which is technically off-label.

In a randomized, vehicle-controlled study, AK clearance rates following 1-, 2-, and 3-hour ALA incubation were all comparable and significantly greater relative to vehicle-PDT. However, moderate-to-severe stinging/burning during PDT was substantially more common with 2- and 3-hour vs 1-hour incubation, as were edema and moderate-to-severe erythema post-PDT (Table 1).[15] Simultaneous light activation of PpIX during ALA incubation (simultaneous protocol) resulted in reduced mean pain scores with nearly identical lesion clearance after 3 months compared with 1-hour ALA incubation (conventional protocol) in a bilaterally controlled study (Table 1).[16] Similarly, 15-min incubation with 20% ALA was associated with little or no pain in patients undergoing blue light PDT for AKs in a single-arm study; in a split-face pilot study, pain was substantially reduced with no loss of efficacy compared with incubation for 75 minutes (Table 1).[17] These results suggest that incubation time can be reduced relative to conventional protocols to improve the tolerability of ALA-PDT without decreasing efficacy.

ALA Formulation

In a randomized, double-blind study, 40 patients with AK on the face or scalp were randomized to treatment with 10% ALA gel or 20% ALA solution with blue light illumination, although 10% ALA gel is labeled for use with red light. Clearance rates were high (≥95%) and comparable; pain scores were lower in patients treated with 20% solution vs 10% gel but not significantly different between groups, although erythema and scaling/dryness were significantly more common following treatment with 20% ALA solution (Table 1).[18]

Light Source

Use of daylight illumination for PDT may be an effective method to minimize pain while maintaining clinical efficacy. The AAD guidelines for treatment of AK conditionally recommend ALA-daylight PDT as less painful but equally effective compared with ALA-red light PDT based on a moderate quality of evidence from a prospective, randomized study in patients with AK of the face or scalp[1] in which pain was significantly greater in patients treated with 10% ALA-red light PDT vs 10% ALA-daylight PDT, with lesion clearance exceeding 95% in both arms (Table 1).[19]

Combined PDT protocols using both daylight and conventional PDT have also been evaluated. In a randomized study of combined PDT vs conventional PDT in patients with AK on the scalp or face, the overall AK clearance rate was slightly higher in the conventional PDT arm, but the clearance rate was not statistically significantly different when lesion clearance was analyzed by grade. Both PDT-associated pain and the severity of erythema and edema were significantly lower in patients who received combined vs conventional PDT (Table 1).[20]

The primary advantage of daylight PDT is the near painlessness of the procedure. Furthermore, use of the sun as a light source is free of cost and saves clinic space and time.[21] Limitations of daylight PDT include dependence on favorable weather conditions and the need for sunscreen to reduce ultraviolet exposure. Potential nonadherence to daylight illumination instructions and patients' inability to manage unpredictable local skin reactions outside the clinic are further challenges. Finally, reimbursement is problematic because FDA labeling specifies the blue light and red light illumination devices to be used with approved ALA products.[2,3]

Recent studies, reviewed in detail elsewhere, have explored simulated daylight (SDL)-PDT using an artificial light source emitting white, blue, yellow, or red light.[21] SDL-PDT is usually

TABLE 1.

Prospective Randomized Clinical Trials Evaluating the Efficacy and Tolerability of Modifications of Conventional ALA-PDT Protocols in Patients With Actinic Keratosis

Study	Design/ Enrolled/ Completed (N)	AK Characteristics	Interventions[a,b]	Efficacy Follow-up	Efficacy Outcomes	Safety/Tolerability Outcomes
Adjunctive measures						
Langan 2006[10]	IP, DB/14/13	Extensive AK lesions Grades 1–3 Scalp	4-h 20% ALA (occluded), 2-h lidocaine 2.5%-prilocaine 2.5% cream, 1000-sec red light PDT 4-h 20% ALA (occluded), 2-h aqueous cream, 1000-sec red light PDT	NA	NA	No significant difference in median pain scores ($P = 0.328$)
Vanaman Wilson 2017[13]	DB/20/19[c]	5–20 AK lesions Face	Oral cetirizine 10 mg daily beginning 3 days prior to ALA-PDT until 3 days posttreatment (7 days); 1-h 20% ALA, 1000-sec blue light PDT Oral placebo daily beginning 3 days prior to ALA-PDT until 3 days posttreatment (7 days); 1-h 20% ALA, 1000-sec blue light PDT	6 mo	LC, mean ± SEM Cetirizine: 7.2 ± 2.9 Placebo: 4.6 ± 2.7 ($P = 0.08$)	No significant differences in investigator assessment of erythema, edema, or crusting at any follow-up time point, or in patient-reported symptoms of pain, itching, tightness, oozing, and crusting at postprocedure Days 7 and 30
Silic 2022[11]	IP, RB/20/18	Disseminated AK Face or scalp	cPDT (4-h 20% ALA, red light) with cold air analgesia (CRIOjet Air Mini) cPDT (4-h 20% ALA, red light) with standard fan	6 mo	Complete CR, patients Cold air: 83% Fan: 89% ($P = 1.0$)	Pain VAS (0–10) during PDT, mean Cold air: 2.7 Fan: 3.7 ($P = 0.003$) No difference in intensity of phototoxic skin reaction at any time point
ALA incubation						
Martin 2016[17]	IP, OL/3/3	Moderate–severe Face	15-min 20% ALA, then 1-h blue light PDT (short protocol) 75-min 20% ALA, then 1000-sec blue light PDT (conventional protocol)	≥8 weeks	CR Short: 52% Conventional: 44%	Maximum pain VAS (0–10), mean (range) Short: 0 (0–0) Conventional: 7 (6–8)
Pariser 2016[15]	RB/235/231	6–20 AK lesions Grades 1 or 2 Face or scalp	1-h 20% ALA, 1000-sec blue light PDT (n = 47) 2-h 20% ALA, 1000-sec blue light PDT (n = 48) 3-h 20% ALA, 1000-sec blue light PDT (n = 47) Vehicle, 1000-sec blue light PDT (n = 46) Most subjects received 2 sessions (Day 0, Week 8)	6 mo	CR, median ± SD 1-h ALA: 67% ± 43% 2-h ALA: 65% ± 36% 3-h ALA: 75% ± 46% Vehicle: 14% ± 44% (all $P < 0.001$ for active treatment vs vehicle)	Moderate–severe stinging/ burning during PDT 1-h ALA: 64% 2-h ALA: 79% 3-h ALA: 79% Vehicle: 0% Edema post-PDT 1-h ALA: 21% 2-h ALA: 42% 3-h ALA: 43% Vehicle: 4% Moderate–severe erythema post-PDT 1-h ALA: 38% 2-h ALA: 58% 3-h ALA: 62% Vehicle: 7%
Kaw 2020[16]	IP, NI/24/23	≥4 AK lesions per side Face or scalp	20% ALA and immediate blue light PDT (30, 45, or 60 min; simultaneous protocol) 1-h 20% ALA, blue light PDT (1000 sec; conventional protocol)	3 mo	NI of simultaneous vs conventional protocol demonstrated based on LC reduction vs BL (scalp, 44% vs 42%; face, 58% vs 59%)	Pain VAS (0–10) during PDT, mean Simultaneous: 0.52 Conventional: 3.57 ($P < 0.001$)

TABLE 1. (CONTINUED)

Prospective Randomized Clinical Trials Evaluating the Efficacy and Tolerability of Modifications of Conventional ALA-PDT Protocols in Patients With Actinic Keratosis

Study	Design/ Enrolled/ Completed (N)	AK Characteristics	Interventions[a,b]	Efficacy Follow-up	Efficacy Outcomes	Safety/Tolerability Outcomes
ALA incubation						
Nestor 2019[18]	DB/40/40	4–8 AK lesions Face or scalp	1-h 20% ALA solution (nonoccluded), 1000-sec blue light PDT 1-h 10% ALA gel (nonoccluded), 1000-sec blue light PDT	84 d	CR (total lesions) 20% ALA solution: 95% (P <0.001 vs BL) 10% ALA gel: 97% (P <0.001 vs BL)	Pain VAS (0–100) for the first PDT treatment, mean 20% ALA solution: 25.4 10% ALA gel: 28.5 Day 3 (20% ALA solution vs 10% ALA gel) Erythema (49% vs 15%; P = 0.002) Crusting (10% vs 5%; P = NS) Scaling/dryness (41.0% vs 10.3%; P = 0.002)
Light source						
Zhu 2018[19]	OL/60/55	Grades 1, 2, or 3 Face or scalp	3 sessions over ~6 weeks: 30-min 10% ALA (occluded), 2-h dl-PDT (dl-PDT arm) 3-h 10% ALA (occluded), red light PDT (100 J/cm²; cPDT arm)	1 mo (following 3rd session)	Lesion CR dl-PDT: 96% cPDT: 97% (P = 0.856)	Maximum pain VAS (0–10) after PDT, mean dl-PDT: 1.7 cPDT: 5.2 (P <0.05)
Sáenz-Guirado 2022[20]	RB, NI/52/50	≥5 AK lesions Grades 1 or 2 Face or scalp	10% ALA, dl-PDT then red light PDT (37 J/cm; combPDT arm) 10% ALA, red light PDT (37 J/cm; cPDT arm)	3 mo	CR (combPDT vs cPDT) Overall: 77% vs 87% (P = 0.017) Grade 1: 77% vs 87% (P = 0.094) Grade 2: 80% vs 83% (P = 0.679)	Pain VAS (1–10) during PDT, mean combPDT: 2.56 cPDT: 5 (P <0.01) LSR severity (0–3) after 24 h, mean (combPDT vs cPDT) Erythema: 1.04 vs 1.58 (P = 0.005) Edema: 0.2 vs 0.56 (P = 0.033) Crusting: 0.32 vs 0.56 (P = 0.524)
Illumination parameters						
Apalla 2011[22]	IP, RB/50/50	≥3 AK lesions Grades 1 or 2 Face or scalp	4-h 20% ALA (occluded), red light PDT 75 J/cm² via fluence rate: 25 mW/cm² 50 mW/cm² 75 mW/cm²	3 mo	Complete CR 25 mW/cm²: 92% 50 mW/cm²: 90% 75 mW/cm²: 92%	Pain VAS (0–10) during PDT, mean 25 mW/cm²: 6.9 50 mW/cm²: 7.0 75 mW/cm²: 8.2 (P <0.001 vs other 2 groups)
Salvio 2021[25]	OL/30/30	Widespread AK Upper limbs	20% ALA and 40-min red light PDT (36 J/cm² fluence): 3-h occluded incubation period (Group 1) 1.5-h occluded incubation period (Group 2) 1.5-h occluded incubation period with 2-min pauses every 10 min during illumination (Group 3)	1 mo	Reduction in LC, mean Group 1: 56% Group 2: 55% Group 3: 66% (P = NS)	Proportions of patients reporting low levels of pain during illumination were highest in Group 3; Group 2 had the highest rates of severe pain

[a]One PDT session unless otherwise noted.
[b]Bold text indicates differences between interventions.
[c]One patient withdrew prior to treatment, leaving 19 patients treated in total.
AK, actinic keratosis; ALA, 5-aminolevulinic acid; BL, baseline; combPDT, combination PDT; cPDT, conventional PDT; CR, clearance rate; DB, double blind; dl, daylight; IP, intrapatient (bilateral control or crossover); LC, lesion count; LSR, local skin reaction; NA, not applicable; NI, noninferiority; NS, nonsignificant; OL, open-label; PDT, photodynamic therapy; RB, rater (or investigator) blinded; SD, standard deviation; SEM, standard error of the mean; VAS, visual analog scale.

performed indoors with a short incubation time, allowing simultaneous light activation of PpIX during PpIX formation and rendering the treatment almost painless.[21] SDL-PDT addresses the weather-, adherence-, and monitoring-related limitations of daylight PDT, but requires a lamp and more time spent in the clinic. Additional research is needed to standardize pretreatment, incubation time, light source, and irradiation time for SDL-PDT.[21] Similar to daylight PDT, reimbursement of SDL-PDT in the US is problematic because light sources are specified in the product labeling.[2,3]

Fluence Rates and Stepped Irradiance

Lower fluence rates (25 and 50 mW/cm^2) were associated with reduced pain compared with a fluence rate of 75 mW/cm^2 in patients with AKs undergoing ALA-PDT, with comparable proportions of patients achieving complete clearance at 3 months (Table 1).[22] Two-step irradiance protocols using low radiances early in the PDT session before progressing to higher radiances have been developed with the aim of minimizing pain,[23,24] but randomized studies in patients with AK are needed.

Brief Pauses During Illumination

A clinical trial evaluated pain and efficacy of different PDT protocols using ALA 20% with red light and incubation for 3 hours (Group 1), 1.5 hours (Group 2), or 1.5 hours with 2-minute pauses every 10 minutes during illumination (Group 3). Proportions of patients reporting low levels of pain during illumination were highest in Group 3, whereas Group 2 had the highest rates of severe pain. Mean reductions in AK lesion count at 30 days were comparable across the 3 groups (Table 1).[25] In the author's experience, pausing at 3-minute intervals may be a more realistic protocol in clinical practice.

DISCUSSION AND CONCLUSIONS

Published recommendations for the management of pain associated with ALA-PDT include the use of cold air analgesia or a fan to cool the skin, short breaks during illumination, intralesional lidocaine injection prior to treatment, or use of topical anesthetics prior to or following treatment.[4] Continuous activation of low levels of PpIX using shorter incubation times, lower irradiance, and daylight or combined PDT may decrease pain without loss of efficacy in AK.[15,16,19,20] However, few modifications to conventional ALA-PDT protocols have been rigorously evaluated in clinical trials, and even fewer are backed by FDA approval. Larger, randomized, controlled studies, particularly those evaluating daylight and combination PDT, are needed to standardize these protocols, strengthen the evidence base, and support reimbursement in AK and other indications.

Our current methods for controlling pain and discomfort during and after ALA-PDT have been informed by the literature reviewed here, as well as clinical experience. Optimization of tolerability begins with taking care to identify patients with contraindications to ALA-PDT. These include patients taking known photosensitizers and those who are unable to avoid light exposure to treated skin for 24 to 48 hours after treatment.[4] For topical pain control, we recommend refrigerated hypochlorous acid spray as a suitable alternative to the adjuncts above, and we anticipate with interest the publication of a recently completed clinical trial evaluating 5% menthol cream for pain reduction during PDT for AK (www.clinicaltrials.gov; NCT02984072). Antihistamines are not approved for the indication, but our practice has found them useful in reducing the immediate edema and itching believed to be caused by the degranulation of mast cells and basophils in response to ALA-PDT.[12] Although controlled clinical trials have not been conducted to evaluate their effectiveness in this setting, anxiolytic therapies (eg, alprazolam) and/or increased time spent with the patient at the beginning of the session ("talk-esthesia") may be effective for reducing pain and discomfort associated with ALA-PDT. In addition, a new antipruritic topical formulation containing aluminum acetate (Dermeleve®, Advanced Derm Solutions, LLC)[26] is useful as an adjunct during pretreatment in the author's experience, although it has not been clinically evaluated in AK. After treatment, the use of a skin-soothing spray (not containing sensitizers like benzocaine) for several days generally helps to manage burning and irritation, and patients should be strongly advised to use sunscreen.[4]

The number of procedural variables involved in ALA-PDT and the range of conditions for which this modality is used confounds the development of standardized protocols to minimize pain and maintain efficacy. However, investment of time and funds toward this effort, as well as a commitment to information sharing among PDT practitioners, has the potential to significantly improve the use and effectiveness of PDT for a range of cutaneous diseases.

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