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Laser-Mediated Photodynamic Therapy of Actinic Keratoses

Macrene R. Alexiades-Armenakas, MD, PhD; Roy G. Geronemus, MD

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ABSTRACT

Objective To assess the safety and efficacy of the long-pulsed pulsed dye laser (LP PDL) (595 nm) with photodynamic therapy (PDT) for treatment of actinic keratoses (AKs).

Design Prospective, controlled study with 10-day and 2-, 4-, 6-, and 8-month follow-ups.

Setting Clinical research center.

Patients Volunteer sample of 41 patients (age range, 35-91 years; skin types I-III) with AKs.

Intervention Single treatment with application of topical 20% 5-aminolevulinic acid for 3 hours or 14 to 18 hours, followed by LP PDL irradiation at 595 nm. Controls received LP PDL irradiation alone.

Main Outcome Measures Safety assessments, treatment and recovery times, and efficacy assessments, including patient mean percentage of lesions cleared and distribution of patients by percentage of lesions cleared for different anatomic sites.

Results We observed no to slight pain; slight to moderate erythema; no purpura, crusting, or scarring; treatment time of 1 lesion per second; and resolution of erythema by 7 to 14 days. The patient mean (95% confidence interval) percentage of head lesions (2620 lesions) cleared after 1 treatment was 99.47% (99.44%-99.50%) at 10 days, 98.19% (98.15%-98.23%) at 2 months, 92.94% (92.73%-93.14%) at 4 months, 91.65% (91.15%-92.15%) at 6 months, and 90.32% (78.10%-100%) at 8 months. For extremities (949 lesions), these were 83.1% (81.4%-84.9%) at 10 days, 75.5% (73.4-77.6) at 2 months, 70.9% (68.9%-72.8%) at 4 months, 92.0% (84.0%-100%) at 6 months, and 100% at 8 months. For trunk (53 lesions), these were 85% (74%-100%) at 10 days, 85% (74%-100%), and 65% (50%-80%) at 4 months. No difference in safety or efficacy was found between the 3-hour and 14- to 18-hour incubation times. In the laser-only control group, no decrease in lesions was observed. Among 31 patients with head lesions, 28 (90%) at 10 days, 19 (70%) at 2 months, 9 (47%) at 4 months, 5 (42%) at 6 months, and 5 (56%) at 8 months were completely (100%) clear following a single treatment. Skin biopsy specimens of nonresponding lesions demonstrated a high rate of squamous cell carcinoma and other non-AK neoplasms.

Conclusions Treatment of AKs using LP PDL (595 nm) at nonpurpuric parameters following topical application of 5-aminolevulinic acid is safe and effective. The advantages may include minimal discomfort, rapid incubation treatment and recovery times, excellent posttreatment cosmesis, high efficacy rates with respect to head lesions, and practical applicability to large body surface areas.

INTRODUCTION

ACTINIC KERATOSES (AKs) are cutaneous neoplasms prevalent in up to 40% to 60% of whites older than 40 years and 80% of whites older than 60 years, which eventuate in squamous cell carcinoma (SCC) at rates up to 10% to 20% per decade.¹⁻⁴ Many therapies for AK exist; however, physicians and patients have reported dissatisfaction with these modalities.⁵ The first category of AK therapies is ablative, including techniques such as curettage and electrodesiccation and cryotherapy. Disadvantages of this approach include hypopigmentation, scarring, and limitation in the body surface area (BSA) treated.⁶ Medium-depth chemical peeling may also be included in this category, but may have significant morbidity, including posttreatment wounding and prolonged erythema. The second category of AK therapies is topical chemotherapy, the prototype being topical fluorouracil, with the recent additions of topical imiquimod and diclofenac. Disadvantages of this approach include the need for high patient compliance (eg, must be applied twice daily for several weeks), marked erythema and crusting, a long recovery period, and high treatment failure rate due to noncompliance.⁷⁻⁸ Pulsed dosing of fluorouracil cream, in which medication is applied 1 or 2 times per week for several months, has been used to diminish adverse effects; however, cure rates may be lower.⁹ The third category of AK therapy is photodynamic therapy (PDT). This treatment entails application of topical 5-aminolevulinic acid (5-ALA) solution for a 14- to 18-hour incubation period, followed by irradiation with a low-energy incoherent blue light source. Recently, another topical photosensitizer, methylaminolevulinate, has been approved in Europe for use with red light in the treatment of AK and basal cell carcinoma. Disadvantages of PDT with incoherent light include pain during the lengthy illumination period, which lasts approximately 16 minutes, and posttreatment erythema and crusting that may persist for weeks.¹⁰⁻¹¹

The objective of this study was to advance PDT with the goals of diminished pain, faster treatment and recovery times, and improved posttreatment cosmesis. To address these goals, we investigated whether other light sources would be effective. The absorption spectrum of protoporphyrin IX, the conversion product of 5-ALA responsible for photodynamic reactions, has a peak in the 585-nm range.¹² In a prior study, the 585-nm long-pulsed pulsed dye laser (LP PDL) (Sclerolase; Candela, Wayland, Mass) was used to treat AK following topical 5-ALA application, with good efficacy, but with cosmetically unacceptable purpura.¹² The hypothesis that the LP PDL at 595 nm (V beam; Candela) would be effective as an alternate light source for PDT was therefore put forth. This laser has the advantages of variable pulse widths extending from 1.5- to 40-millisecond (ms) pulse durations in the nonpurpuric range, large spot size, dynamic cooling device to diminish pain, and rapid treatment time, operating at 1 Hz. Given these advantages, the LP PDL was assessed in conjunction with PDT using topical 20% 5-ALA in the treatment of AKs.

METHODS

Forty-one adult (16 women and 25 men; mean [range] age, 70 [35-91] years; skin phototypes I-III) with AKs, defined as erythematous hyperkeratotic, scaling patches, papules or plaques on the head, extremities, and trunk, were enrolled. Verbal and written informed consent regarding the potential benefits and risks of the procedure was obtained from each subject. Subjects were informed that the treatment is part of a protocol and that the combination of topical 5-aminolevulinic acid solution with the LP PDL was not yet approved by the Food and Drug Administration (FDA), although it had approved both for use independently. Pretreatment lesional counts and photographs were obtained. Pretreatment and posttreatment 3-mm punch biopsy specimens were obtained in 3 patients. Topical 20% 5-ALA hydrochloride solution (Levulan Kerastick; DUSA Pharmaceuticals Inc, Wilmington, Mass) was applied to lesions as detailed in the package insert for incubation times of 3 hours with occlusion with nonadhesive gauze or 14 to 18 hours without occlusion. Initially, patients received the 14- to 18-hour incubation time as described in the package insert; subsequently, patients were randomized to receive either the 3- or the 14- to 18-hour incubation. In cases in which numerous lesions were present, the solution was applied to the entire anatomic area. Surgical lubricant jelly was applied to hyperkeratotic lesions prior to laser treatment. Following a test spot on the volar forearm to assess for purpura, each lesion was subsequently irradiated with 1 to 4 nonoverlapping pulses of the LP PDL at 595 nm (V beam) at fluences of 4 to 7.5 J/cm², a pulse duration of 10 ms, 10-mm spot size, with a 30-ms cryogen spray application followed by a 30-ms delay prior to each laser pulse. Patient and investigator pain assessments were recorded on a 4-point pain scale (0 = no, 1 = slight, 2 = mild, 3 = moderate, and 4 = severe). Adverse effects including stinging, burning, erythema, purpura, blistering, or crusting were recorded on patient and investigator assessment scales (0-4, as above). Time to healing without residual erythema was recorded. Patients were followed up at 10 days and 2, 4, 6, and 8 months for lesion counts, 3-mm punch biopsies, and photographs. Individual lesions were monitored by means of landmarks and photographs whenever possible; however, in most cases the number of lesions present at baseline and at each follow-up interval was counted. Following treatment, skin biopsies of residual lesions were performed. Five patients were enrolled in the control group and received LP PDL treatment alone at the parameters indicated above. The control subjects were consecutively recruited in a nonrandomized manner, and informed consent was obtained. Control subjects received treatment for their AKs after a 1-month follow-up period.

RESULTS

The total number of lesions treated in the experimental group (n = 36) was 3622, with a mean (range) of 98 (1-300) per patient. Anatomic sites included the head (2620 lesions), extremities (949 lesions), and trunk (53 lesions). Pretreatment skin biopsy specimens from 3 patients with representative lesions showed the hallmark histologic findings of AK. Among the 5 patients in the control group, the total number of lesions was 528 (453 on the head and 75 on the extremities).

Safety assessments demonstrated that stinging/burning following 5-ALA application was scored as 0 (no) in 11 patients (31%), 1 (slight) in 19 patients (53%), 2 (mild) in 3 patients (8%), and 3 (moderate) in 2 patients (6%). Pain during laser treatment was scored as 0 in 18 patients (50%), 1 in 13 patients (36%), 2 in 3 patients (8%), and 3 in 1 patient (3%). Erythema following 5-ALA application was scored as 1 in 20 patients (56%), 2 in 13 patients (36%), and 3 in 3 patients (8%). There was no significant increase in erythema following laser irradiation. Severe (score of 4) stinging/burning, pain, and erythema occurred in 1 patient (3%) who, following the 14- to 18-hour 5-ALA application, was inadvertently exposed to several hours of bright sunlight prior to laser therapy. No purpura, crusting, or scarring occurred in any patient. Treatment time was up to 60 lesions per minute (at 1 Hz) and 5 or less minutes in all patients. The slight to moderate erythema was completely resolved by 5 to 10 days in all patients. Among the laser-only controls, pain was scored as 0 to 1 and erythema, 1 to 3, which resolved within 1 day.

Clinical examples of safety and efficacy outcome for 3 representative patients are shown in [Figure 1](#), [Figure 2](#), and [Figure 3](#). Erythematous, keratotic papules and patches were noted at baseline ([Figure 1A](#), [Figure 2A](#), and [Figure 3A](#)). Following topical 5-ALA application, slight to moderate erythema was observed ([Figure 1B](#)), which did not increase significantly after laser treatment ([Figure 1C](#), [Figure 2B](#), and [Figure 3B](#)). At 10-day, 2-month, and 4-month follow-ups, most head AKs remained clear ([Figure 1D](#), [Figure 2C](#), and [Figure 3C](#)).

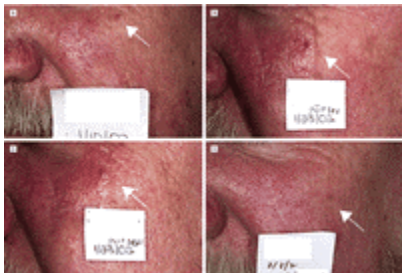


Figure 1. Representative clinical example of treatment of actinic keratosis by application of topical 20% 5-aminolevulinic acid followed by long-pulsed pulsed dye laser irradiation. A, Prior to treatment a keratotic erythematous papule was present on the left cheek of a man with type I skin (arrow). B, Following 5-aminolevulinic acid application, mild erythema was noted at the site of the actinic keratosis (arrow). C, The mild erythema did not increase appreciably following laser irradiation (arrow). D, The erythema resolved fully by posttreatment day 14 (arrow).

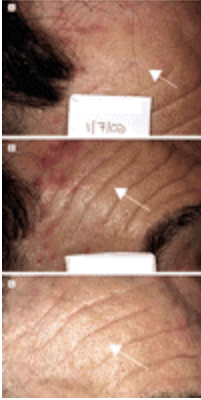


Figure 2. A, Multiple actinic keratoses (AKs) on the right forehead in a man with type II skin are shown prior to treatment (arrow). B, Following topical 5-aminolevulinic acid and laser treatment, mild erythema was noted at the previously identified AK sites (arrow), as well as at sites of subclinical AKs. C, The AKs were clear at the 2-month follow-up interval (arrow).

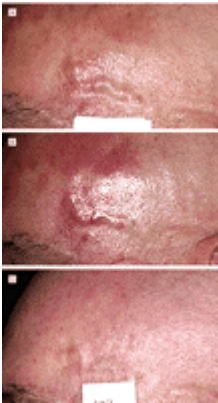


Figure 3. A, Extensive, confluent actinic keratoses across the forehead and scalp of a man with type I skin. B, Following topical 5-aminolevulinic acid and laser treatment, moderate erythema was noted across the forehead and scalp, which resolved by 10-day follow-up. C, At 2-month follow-up, the forehead and scalp were clear of lesions.

Efficacy rates for AK treatment are most often assessed as the number and percentage of AKs cleared. The patient mean percentage of lesions cleared by site at designated times, stratified according to anatomic site, are presented in [Figure 4](#) and [Table 1](#). The safety and efficacy of the treatment after 3-hour vs 14- to 18-hour application times were compared and found to be similar. The difference (95% confidence interval) in patient mean percentage of lesions cleared in the 3-hour and 14- to 18-hour groups is presented in [Table 2](#). The percentage of lesions cleared following 1 treatment, stratified according to anatomic site, are presented in [Figure 5](#) and [Table 3](#). The distribution of patients by percentage of lesions cleared at designated times is presented in [Table 4](#).

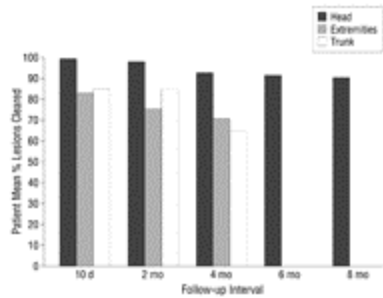


Figure 4. Patient mean percentage of lesions cleared by anatomic site at designated times following a single treatment with topical 5-aminolevulinic acid and long-pulsed pulsed dye laser.

Table 1. Patient Mean Percentage of Lesions Cleared by Site at Designated Times Following a Single Treatment With Topical 5-ALA and LP PDL

Table 2. Difference (95% CI) Between Patient Mean Percentage of Lesions Cleared in Patients With 3-Hour and 14- to 18-Hour Incubation Periods*

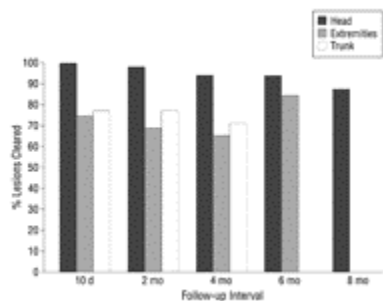


Figure 5. Percentage of lesions cleared by anatomic site at designated times following a single treatment with topical 5-aminolevulinic acid and long-pulsed pulsed dye laser.

Table 3. Percentage of Lesions Cleared by Site at Designated Times Following a Single Treatment With Topical 5-ALA and LP PDL

Table 4. Distribution of Patients by Percentage of Lesions Cleared at Designated Times Following a Single Treatment With Topical 5-ALA and LP PDL*

Among the 5 patients in the laser-only control group, no decrease in lesion counts was observed at 10-day and 1-month follow-ups. Baseline lesion counts were 528 in this group, with a patient mean of 106. At 1-month follow-up, these counts were 530 lesions, with a patient mean of 106.

Findings from pretreatment skin biopsies that were performed in 3 patients demonstrated AK, and posttreatment biopsy findings of the cleared lesion sites demonstrated normal skin. Lesions that did not respond or recurred during the follow-up interval were categorized as treatment failures. Skin biopsies were performed on 30 such lesions among 8 patients. These lesions tended to be larger (>2 mm), thicker, or more keratotic. The histopathologic results were as follows: 11 SCC, 8 AK or hyperplastic AK, 1 basal cell carcinoma, 1 verruca, 1 lichen planus-like keratosis, 1 seborrheic keratosis, and 1 atypical fibroxanthoma. Although this

subgroup may not be representative of the entire group of treatment failures, 16 (67%) were non-AK neoplasms (11 [69%] of these were SCC) and the remaining 8 (33%) were AK or hyperplastic AK ([Table 5](#))

COMMENT

This novel advance of laser-mediated PDT using the LP PDL appears to be a safe, effective, and practical treatment for patients with multiple AKs. Disadvantages to ablative treatment modalities have included risks of hypopigmentation and scarring and a limit to the number of lesions and extent of BSA one can feasibly treat.⁵⁻⁶ Topical agents have the disadvantages of need for high patient compliance, daily applications for weeks, marked erythema and crusting, a long recovery period, and high treatment failure rate.⁷⁻⁸ This approach is not readily tolerated by patients who are active in the workplace or elderly patients. The disadvantages of PDT with the blue light are moderate discomfort, a lengthy treatment period, posttreatment erythema and crusting, and a prolonged recovery time.¹¹ In contrast, laser-mediated PDT may provide the advantages of minimal discomfort, rapid treatment of large numbers of lesions and large surface areas, rapid recovery time, improved posttreatment cosmesis, as well as less risk of hypopigmentation and scarring. Although small numbers of lesions are easily and effectively treated with cryotherapy, laser-mediated PDT is a practical approach to treating large numbers of lesions and large BSAs, such as entire head (9% BSA), extremities (18% BSA), or trunk (36% BSA). One may target a few lesions with several pulses and as many as an entire anatomic area such as head or extremities in less than 5 minutes. By contrast, PDT with blue light would require turning the patient over to expose different sites, taking over 30 minutes or longer in many instances. In addition, the data presented here demonstrate that a short 5-ALA incubation time of 3 hours in conjunction with LP PDL is as effective as the 14- to 18-hour incubation time in clearing AKs, decreasing overall treatment time even further.

Several lasers have been used in conjunction with PDT to treat skin cancer. These have included the gold vapor laser (628 nm), dye lasers pumped by copper vapor, and Nd:YAG and argon ion lasers with emission at 630 nm. They have been used with topical 20% 5-ALA to treat superficial and nodular basal cell carcinoma, Bowen disease, AK, verruca vulgaris, condyloma acuminatum, and keratoacanthoma.¹³⁻¹⁴ Laser treatment of AK with PDT has been performed with argon-pumped dye (630 nm) and LP PDL (585 nm), with clearance rates of 84% at 24- to 36-month follow-up and 79% at 1-month follow-up, respectively.^{13, 15} The disadvantages of these laser systems include scarring with respect to the argon laser and purpura with respect to the LP PDL (585 nm) (Sclerolase).

The rationale for using the LP PDL as a light source for PDT is based on the absorption spectrum of the photosensitizer and the laser's features of variable pulse width, dynamic cooling device, and fast operation speed. As stated previously, a peak near 585 nm is present in the absorption spectrum of the protoporphyrin IX, which is the conversion product of 5-ALA responsible for the photodynamic reactions.¹² The variable pulse width of the LP PDL extending from 1.5- to 40-ms pulse durations allows one to avoid the cosmetically unappealing adverse effect of purpura when used in the nonpurpuric range of 6 to 40 ms. The dynamic cooling device, which involves a spray of liquid cryogen prior to the laser pulse, has been previously shown to dramatically diminish pain with PDL treatment.¹⁶ The minimal discomfort with the LP PDL using the dynamic cooling device in the present study confers an important advantage over the blue light for PDT, which is associated with significant discomfort during the lengthy illumination period. The operation speed of the LP PDL at 1 Hz allows for lesions to be treated rapidly at a rate of up to 60 per second; entire scalp and face treatments were performed in 5 minutes or less. This is an additional advantage in treatment time over all other modalities. The potential limitations of this

approach relate mainly to those of PDT in general, such as phototoxic reactions, its restricted use to sites with low hair density, and avoidance of the periorbital region.

Efficacy rates of laser-mediated PDT were high with respect to head lesions and comparable with other AK treatment modalities. Although a cure rate from cryosurgery as high as 98% has been frequently cited, this was a retrospective study lacking quantitative analysis.¹⁷ The published studies using topical fluorouracil to treat AK date back several decades, are anecdotal, do not contain efficacy rates, and report recurrence rates of approximately 25% to 50% over a 24- to 36-month follow-up.¹⁸⁻²⁰ In a recent study evaluating pulse dosing of topical fluorouracil weekly over an average of 6.7 weeks, 6 patients were followed up to 9 months, with an 86% clearance rate.²¹ In a published trial for PDT with blue light, which studied 36 patients, the efficacy rate for percentage of head AKs cleared after a single treatment was 66% at 8 weeks.¹¹ In contrast, the efficacy rate for patient mean percentage of head AKs completely cleared following a single treatment of LP PDL-mediated PDT in our study of 36 patients was 99.47%, 98.19%, 92.94%, 91.65%, and 90.32% after 10 days and 2, 4, 6, and 8 months, respectively.

Extremity AKs have been generally less responsive to treatment. The studies of topical fluorouracil to treat AK indicate that extremities require 8 weeks of twice-daily application, as opposed to 2 to 4 weeks on the face.¹⁸⁻²⁰ One prior report comparing PDT with incoherent red light (580-740 nm) and topical fluorouracil in treatment of extremity AKs showed a mean reduction in lesional area of 73% with PDT and 70% with fluorouracil at 6-month follow-up.¹⁰ No patient showed complete clearing of AKs with either treatment. In the present study, LP PDL-mediated PDT in the treatment of extremity AKs resulted in patient mean percentage of lesion clearance rates of 83.1%, 75.5%, and 70.9% and percentage of lesion clearance rates of 75.2%, 68.8%, and 65.2% at 10-day, 2-month, and 4-month follow-up, respectively. Complete clearing of extremity AKs using LP PDL-mediated PDT was achieved in 60%, 40%, and 17% at 10-day, 2-month, and 4-month intervals, respectively. These preliminary data suggest improved clearing of extremity AKs with LP PDL-mediated PDT, which may be in part due to greater penetration of the 595-nm wavelength compared with blue light in the 417 ± 5 -nm range.

The efficacy rates presented here are likely to be lower than the true efficacy for the following reasons: First, 7 patients enrolled in the study had failed prior treatment with cryotherapy and topical fluorouracil. Second, the numbers reported are largely a comparison of the number of lesions present on follow-up relative to baseline, and new lesions may appear over time. Finally, lesions in which LP PDL-mediated PDT treatment had failed were in many cases SCC or other neoplasms. Among the 24 nonresponder lesions analyzed histopathologically, 67% were non-AK neoplasms, and most of these (69%) were SCC. The finding of 11 SCCs among nonresponders of 3622 lesions treated suggests an accurate pretreatment assessment and supports the theory of a biological continuum of AK and SCC. It has been concluded that "it can be impossible to distinguish between an actinic keratosis and squamous cell carcinoma."²² Nonresponder lesions tended to be larger and more keratotic, and the biopsy results indicate some underestimation of true efficacy of AK clearing. This approach may be useful in distinguishing between AKs and skin cancers in patients with numerous and confluent skin lesions. In light of these data, we recommend that biopsies be performed for nonresponding lesions that are large (>5 mm) and hyperkeratotic.

CONCLUSIONS

Laser-mediated PDT for the treatment of AKs using the LP PDL (595 nm) at nonpurpuric parameters following topical 5-ALA application with short (3-hour) or long (14-18-hour) incubation time is safe and effective and may provide numerous advantages. These include minimal discomfort, rapid treatment and recovery times, excellent posttreatment cosmesis, high efficacy rates with respect to head lesions, and practical applicability to large BSA. A randomized, vehicle- and LP PDL-controlled, double-blinded study is under way at our center to further investigate laser mediated-PDT in the treatment of AKs, rhytides, and photodamage.

AUTHOR INFORMATION

Corresponding author and reprints: Macrene Alexiades-Armenakas, MD, PhD, Laser & Skin Surgery Center of New York, 317 E 34th St, New York, NY 10016 (e-mail: mralexides@yahoo.com and mail@laserskinsurgery.com).

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