CO_2 Laser Ablative Fractional Resurfacing Photodynamic Therapy for Actinic Keratosis and Nonmelanoma Skin Cancer: A Randomized Split-Side Study

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PRACTICE **POINTS**

- Pretreatment with CO_2 laser ablative fractional resurfacing (AFR) before photodynamic therapy (PDT) provided efficient clearance of actinic keratosis (AK).
- Superior clearance of lesions was seen at 6 months for AK and thin nonmelanoma skin cancers (NMSCs) on pretreated sites compared to PDT alone, with no novel adverse events reported.
- A reduced incubation period for aminolevulinic acid (ALA) absorption before PDT was used, leading to a shorter overall treatment time.

Aminolevulinic acid (ALA) photodynamic therapy (PDT) is a preferred method for treatment of multiple actinic keratoses (AKs) in broad skin areas (referred to as field cancerization). Pretreatment with CO_2 laser ablative fractional resurfacing (AFR) may increase the efficacy of PDT. This study compared the effect and durability of CO_2 laser AFR-assisted ALA-PDT vs ALA-PDT alone in the treatment of AKs and nonmelanoma skin cancers (NMSCs) at various body locations. In this randomized, split-side study, 19 patients had 1 side pretreated with AFR before treatment of both sides with ALA-PDT. Results indicated that pretreatment with AFR provided superior clearance of AKs and thin NMSCs at 6 months compared to ALA-PDT alone.

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Actinic keratosis (AK) is the most common cutaneous lesion and is regarded as a precursor to nonmelanoma skin cancer (NMSC), particularly squamous cell carcinoma (SCC).[1] Field cancerization refers to broad areas of chronically sun-exposed skin that show cumulative sun damage in the form of clinical and subclinical lesions. It is not feasible to treat large areas with multiple overt and subclinical lesions using surgical methods, and photodynamic therapy (PDT) has become a preferred method for treatment of field cancerization.[2] Topical PDT uses the heme biosynthesis pathway precursors aminolevulinic acid (ALA) or methyl ALA (MAL), which localizes in the treatment area and is metabolized to protoporphyrin IX.[3] After an incubation period, activation by a light source results in the formation of cytotoxic oxygen species,[4] with reports of efficacy over large areas and excellent cosmetic outcomes.[2]

Laser ablative fractional resurfacing (AFR) also has been investigated as a treatment of AKs; CO_2 laser AFR treatment resulted in a short-term reduction in the number of AK lesions and appeared to reduce the development of new lesions.[5] However, case reports and small studies have indicated that pretreatment with laser AFR can increase the efficacy of PDT by creating microscopic vertical channels facilitating deeper penetration and uptake of the ALA.[6] The use of erbium:YAG lasers in combination with PDT has demonstrated notable clinical and aesthetic improvements in treating basal cell carcinomas (BCCs)[7] and AKs,[8] with enhanced efficacy in moderate to thick AKs in particular. Hædersdal et al[6] reported that CO_2 laser AFR facilitated delivery of MAL into porcine skin, with AFR appearing to bypass the stratum corneum and deliver the treatment to the deep dermis.

The combination of CO_2 laser AFR and PDT has shown statistically significant increases in efficacy for treatment of AKs compared to PDT alone ($P<.001$).[9] In a small study, Alexiades[10] reported a statistically significant improvement in AKs at 4 and 8 weeks posttreatment

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for 10 patients receiving CO_2 laser AFR-PDT vs conventional PDT ($P<.05$). Studies of organ transplant recipients—who are at higher risk for AK and NMSC development—demonstrated favorable results for combined CO_2 laser AFR and PDT vs either laser treatment[11] or PDT[9,12] alone, with significant reductions in the number of AKs ($P=.002$). Results were maintained for 3 to 4 months after treatment. Additional studies have shown that combining CO_2 laser AFR and PDT may reduce the PDT incubation time or number of treatments required to achieve a response over conventional PDT.[13,14]

Our proof-of-concept study was designed to assess efficacy of CO_2 laser AFR to enhance an approved drug delivery system in the treatment of AK and NMSC. The objective was to compare effect and durability of AFR-PDT vs standard ALA-PDT in the treatment of AK and NMSCs in a split-sided study of various body locations.

Methods

This randomized, split-sided study compared CO_2 laser AFR-PDT to standard ALA-PDT for the treatment of AK and NMSC conducted at 1 site in Los Gatos, California. Patients who had a skin cancer screening and received a biopsy diagnosis of AK or NMSC were invited to attend an enrollment visit. Key inclusion criteria for enrollment were male or female patients aged 40 to 85 years with notable symmetrically comparable photodamage (at least 1 AK per square centimeter) in 1 or more skin areas—scalp, face, or distal extremities—with presence of clinically identifiable NMSCs proven by biopsy. Key exclusion criteria were patients who were pregnant; patients with epilepsy, seizures, or a photosensitive disorder; those taking photosensitizing medication (eg, doxycycline, hydrochlorothiazide); or immunocompromised patients. The study was approved by an institutional review board (Salus IRB [Austin, Texas]), and each participant underwent a complete and informed consent process.

Laterality for pretreatment with AFR followed by ALA-PDT vs ALA-PDT alone was determined at the time of treatment using a computer-based random number generator; even numbers resulted in pretreatment of the right side, and odd numbers resulted in pretreatment of the left side. Because of the difference in pretreatment methods for the 2 sides, it was not possible to perform the procedure under blinded conditions.

The treatment area was prepared by defatting the entire site with 70% isopropyl alcohol, followed by benzalkonium chloride antibacterial cleansing for the AFR pretreatment side. A 7% lidocaine/7% tetracaine ointment was applied under polyethylene wrap occlusion to the AFR pretreatment side for 20 minutes. Additionally, nerve blocks and field blocks with a mixture of 1.1% lidocaine with epinephrine/0.5% bupivacaine with epinephrine were performed wherever feasible. After 20 minutes, the lidocaine-tetracaine ointment was removed with isopropanol, and AFR treatment commenced immediately with the SmartXide DOT laser (DEKA)(1 pass of 25 W, 1200-microsecond duration at 500-µm spacing, 200-µm spot size, achieving 12% surface area ablation). Hyperkeratotic treated areas were debrided with saline and received a second pass with the laser. Aminolevulinic acid solution 20% (Levulan Kerastick; DUSA Pharmaceuticals, Inc)[15] was applied to both sides of the treatment area and allowed to absorb for a 1-hour incubation period, which was followed by blue-light exposure at a power density of 10 mW/cm^2 for 16 minutes and 40 seconds using the BLU-U Photodynamic Therapy Illuminator (DUSA Pharmaceuticals, Inc). Areas treated with AFR were then covered with a layer of Aquaphor ointment (Beiersdorf, Inc) and an absorptive hydrogel dressing for 48 to 96 hours, with continued application of the ointment until resolution of all crusting. After treatment, patients were instructed to avoid direct sun exposure, wear a hat or visor for the first 2 weeks posttreatment when outdoors, and apply sunscreen with a sun protection factor greater than 30 once skin had healed.

Follow-up was conducted at 1 week, 1 month, 3 months, and 6 months after the PDT procedure. The primary end points were clinical clearance of NMSC lesions at 1, 3, and 6 months posttreatment and histological clearance at 6 months. Secondary end points assessed quality of life and functional improvements.

Results

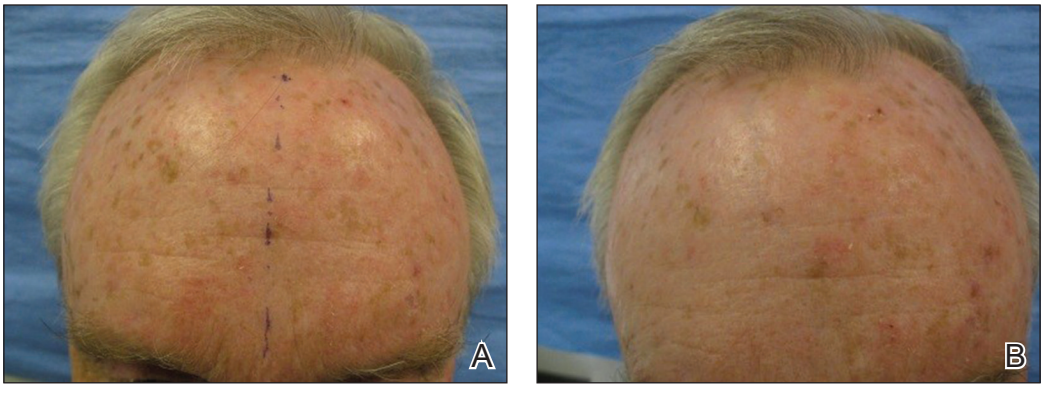
Twenty-four potential participants experiencing AKs and/or NMSCs were screened for the study, with 19 meeting inclusion criteria. All participants were white, non-Hispanic, and had Fitzpatrick skin types I or II. Treated areas for all participants had field cancerization defined as at least 1 AK per square centimeter. All 19 participants enrolled in the study completed the posttreatment evaluations up to 6 months. All AFR-pretreated sites showed superior results in reduction in number, size, or hyperkeratosis of AKs at all follow-up visits, with a complete absence of new AK formation at the 6-month follow-up (Table). Conversely, sites treated with standard PDT only showed some recurrence of AKs at 6 months. Of the 3 participants who had biopsy-confirmed BCCs on the AFR-pretreated side, there were 3 persistent lesions after treatment at the 6-month visit. Two participants experienced persistence of a confirmed SCC in situ that was on the laser-pretreated side only (1 on the forehead and 1 on the hand), whereas 1 participant with an SCC on the leg at baseline had no recurrence at 6 months. A participant who received treatment on the lower lip had persistence of actinic cheilitis on both the AFR- and non–AFR-treated sides of the lip.

Scalp and facial sites healed fully in an average of 7 days, whereas upper extremities—forearm and hands—took approximately 14 days to heal completely. Lower extremity AFR-pretreated sites exhibited substantial weeping, resulting in prolonged healing of approximately 21 days for resolution of all scabbing. Pain during

TABLE. Recurrence of AKs and SCC/BCC at 6 Months[a]

Site	Diagnosis	Pretreated Side	6-mo Response	
			AFR-PDT	Standard PDT
Full face	BCC, AK	Left	1 persistent BCC[b]	1 persistent BCC
Full face	BCC, AK	Right	Persistence of 2 nodular BCCs	No BCC present at baseline or 6 months; persistent AKs
Scalp	AK	Left	No recurrence of AKs	Persistence of AKs
Scalp	AK	Left	No recurrence of AKs	Persistence of AKs
Scalp	AK	Left	No recurrence of AKs	Persistence of AKs
Scalp	AK	Front	Superior result on the AFR-PDT–pretreated area	
Forehead	SCC, AK	Right	Persistence of SCCIS[c]; no AKs	No NMSC present at baseline or 6 mo; multiple AKs present
Forehead	AK	Right	Superior result on the AFR-PDT–pretreated side	
Temple	AK	Right	Superior result on the AFR-PDT–pretreated side	
Lower lip	AK	Right	Persistence of actinic cheilitis on both sides of lip	
Forearm	AK	Left	No recurrence of AKs	Persistence of AKs
Forearm	AK	Left	No recurrence of AKs	Persistence of AKs
Hand	AK	Left	No recurrence of AKs	Persistence of AKs
Hand	AK	Right	No recurrence of AKs	Persistence of AKs
Hand	AK	Right	No recurrence of AKs	Persistence of AKs
Hand	SCC, AK	Right	1 persistent SCCIS[c] and several persistent AKs	No SCCIS at baseline or 6 mo; persistence of AKs
Hand	AK	Right	No recurrence of AKs	Persistence of AKs
Hand	AK	Left	No recurrence of AKs	Persistence of AKs
Leg	BCC, AK	Left	No recurrence of sBCCs	Persistence of BCC lesions
Leg	SCC, AK	Right	No recurrence of SCCs or SCCIS; no AKs	No SCC or SCCIS at baseline or 6 mo; multiple clinical AKs

Abbreviations: AK, actinic keratosis; SCC, squamous cell carcinoma; BCC, basal cell carcinoma; AFR, ablative fractional resurfacing; PDT, photodynamic therapy; SCCIS, squamous cell carcinoma in situ; NMSC, nonmelanoma skin cancers; sBCC, superficial basal cell carcinoma.
[a]Nineteen patients were treated; 1 patient had 2 sites treated.
[b]Two lesions resolved.
[c]Biopsy confirmed.



A, A patient with actinic keratosis who was randomized to receive laser ablative fractional resurfacing pretreatment on the right side of the forehead. B, At 6 months posttreatment, skin was smoother and more elastic with decreased lentiginosis and more uniform color.

treatment was mild to moderate, as field blocks with local anesthesia and topical anesthetic were used prior to AFR treatment. No novel adverse events were reported in the combined use of laser AFR and PDT; all adverse events noted have been recorded in studies of the separate techniques.[16,17]

Comment

In this split-sided study in patients with field cancerization, the use of CO_2 laser AFR before treatment with PDT increased AK lesion clearance compared to ALA-PDT alone. Prior studies of fractional laser–assisted drug delivery on porcine skin using topical MAL showed that laser channels approximately 3-mm apart were able to distribute protoporphyrin through the entire skin.[6] The ablative nature of AFR theoretically provides deeper and more effusive penetration of the ALA solution than using conventional PDT or erbium:YAG lasers with PDT.[7,8] Helsing et al[11] applied CO_2 laser AFR MAL-PDT to AKs in organ transplant recipients and obtained complete responses in 73% of patients compared to a complete response of 31% for AFR alone. The results reported in our study are consistent with Helsing et al,[11] showing a complete clinical response for 14 of 19 patients (74%), of whom 4 (21%) had no recurrence of NMSC and 10 (53%) had no recurrence of AK on the AFR-PDT–treated side.

The pretreatment process required for the laser AFR added time to the initial visit compared to conventional PDT, which is balanced by a reduced PDT incubation time (1 hour vs the approved indication of 14–18 hours for face/scalp or 3 hours for upper extremities under occlusion). The use of microneedling as an alternative pretreatment procedure before PDT also has been investigated, with the aim of decreasing the optimum ALA absorption time. The mean reduction in AKs (89.3%) was significantly greater than for PDT alone (69.5%; $P<.05$) in a small study by Spencer and Freeman.[18] Although microneedling is less time-intensive and labor-intensive than laser AFR, the photocoagulative effect and subsequent microhemorrhages resulting from AFR should result in much deeper penetration of ALA solution than for microneedling.

The limitations of this proof-of-concept study arose from the small sample size of 19 participants and the short follow-up period of 6 months. Furthermore, the unblinded nature of the study could create selection, detection, or reporting bias. Further follow-up appointments would aid in determining the longevity of results, which may encourage future use of this technique, despite the time-consuming preparation. A larger study with follow-up greater than 1 year would be beneficial, particularly for monitoring remission from SCCs and BCCs.

Conclusion

Pretreatment with CO_2 laser AFR before ALA-PDT provided superior clearance of AKs and thin NMSCs at 6 months compared to ALA-PDT alone (Figure). Additionally, the incubation period for ALA absorption can be reduced before PDT, leading to a shorter treatment time overall. The benefits of AFR pretreatment on AK clearance demonstrated in this study warrant further investigation in a larger trial with a longer follow-up period to monitor maintenance of response.

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