Topical 5-Aminolevulinic Acid Combined With Intense Pulsed Light in the Treatment of Photoaging

Jeffrey S. Dover, MD, FRCPC; Ashish C. Bhatia, MD; Brigitte Stewart; Kenneth A. Arndt, MD

Background: The adjunctive use of 5-aminolevulinic acid (5-ALA) with intense pulsed-light (IPL) treatments has been suggested to increase the benefit of IPL for photoaging; however, to our knowledge, no controlled trials have been performed.

Design: A prospective, randomized, controlled, split-face study was designed. Twenty subjects participated in a series of 3 split-face treatments 3 weeks apart in which half of the face was pretreated with 5-ALA followed by IPL treatment while the other half was treated with IPL alone. Two additional full-face treatments (with IPL alone) were then delivered 3 weeks apart. Assessment of global photodamage, fine lines, mottled pigmentation, tactile roughness, and sallowness (on a scale of 0-4) was performed by a blinded investigator before each treatment and 4 weeks after the final treatment. Patients also completed an assessment at the conclusion of the study comparing their results with pretreatment photographs.

Results: All 20 volunteers completed the study. Pretreatment with 5-ALA resulted in more improvement in the global score for photoaging (16 [80%] subjects vs 9 [45%] subjects; \( P = .008 \)) and mottled pigmentation (19 [95%] subjects vs 12 [60%] subjects; \( P = .008 \)) than IPL treatment alone. More successful results were achieved on the side pretreated with 5-ALA compared with the side treated with IPL alone for fine lines (12 [60%] subjects vs 5 [25%] subjects; \( P = .008 \)) and mottled pigmentation (17 [85%] subjects vs 4 [20%] subjects; \( P < .001 \)). While there was noticeable improvement over baseline scores with respect to tactile roughness and sallowness, pretreatment with 5-ALA did not seem to enhance the results of the IPL treatment. The final investigator cosmetic evaluations (\( P = .0002 \)) and subject satisfaction scores (\( P = .005 \)) were significantly better for the 5-ALA-pretreated side. Both treatments were well tolerated, with little difference in the incidence or profile of adverse effects with or without 5-ALA pretreatment.

Conclusions: The adjunctive use of 5-ALA in the treatment of facial photoaging with IPL provides significantly greater improvement in global photodamage, mottled pigmentation, and fine lines than treatment with IPL alone, without a significant increase in adverse effects. This combination treatment enhances the results of photorejuvenation and improves patient satisfaction.

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TREATMENTS WITH INTENSE pulsed light (IPL) are a well-recognized, convenient, frequently performed therapy for photoaged skin. They are used to improve pigmentary changes, telangiectasia, and skin texture. Individual treatments with IPL devices (500-1200 nm) have been used for the treatment of telangiectasia and erythema, the reduction of lentigines, and the dyspigmentation of photoaging for more than 10 years. More recently, a series of 4 to 6 IPL treatments termed photorejuvenation has been popularized. After these low-intensity treatments, the greatest improvement is seen in lentigines, slightly less improvement is seen in facial redness and telangiectasia, and even less improvement is seen in overall skin tone. Minimal improvement of fine lines and wrinkles is achieved, and improvement in pore size is also limited. The desirable results and safety of IPL treatments have made it a favorite modality for nonablative therapy. At least 5 manufacturers actively market IPL devices in the United States, and further research on refining this modality is proceeding briskly.

The adjunctive use of topical 5-aminolevulinic acid (5-ALA) pretreatment with IPL treatments has been suggested to

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enhance the therapeutic effect of IPL on photaging, but, to our knowledge, no controlled trials have been performed to confirm this concept.\(^3\)

## METHODS

Twenty patients were recruited from a single group practice for this prospective, single-blinded, split-face study. The patients were randomized as to which side of their face would be treated with IPL and topical 5-ALA solution (Levulan Kerastick; DUSA Pharmaceuticals, Inc, Wilmington, Mass) vs IPL alone. The study protocol and informed consent form were submitted and approved by the Western Institutional Review Board, Olympia, Wash. All 20 patients consented to participation in the study and were provided a copy of the consent form.

### PATIENT CHARACTERISTICS

The indication for treatment for all patients was photaging. The mean age of the patients was 55 years (range, 45-70 years). The skin types of the patients were I through IV. The patients in the study were all white. All patients had at least a modest degree of photaging as defined by a Global Score for Photaging of 2 or more (evaluated on a 0-4 scale).

### LIGHT SOURCE SYSTEM

A single broadband, filtered, IPL source (IPL Quantum SR; Lumenis, Inc, Santa Clara, Calif) with a wavelength from 515 to 1200 nm was used to treat all patients. The standard skin rejuvenation head was used. Program 1 was used on the device, with the first pulse set at 2.4 milliseconds and the second pulse set at 4.0 milliseconds, with a 15-millisecond delay between pulses. The fluence ranged from 23 to 28 J/cm\(^2\). All of the subjects received a fluence of 26 J/cm\(^2\) at the initial treatment. Based on tolerability, the second treatment fluence was between 24 and 28 J/cm\(^2\) and the third treatment between 26 and 28 J/cm\(^2\). Half of the subjects had the fluence increased from 26 to 28 J/cm\(^2\) at the second treatment; 2 subjects had the fluence decreased to 24 J/cm\(^2\). The remaining subjects received the same fluence as in the initial treatment. The fluence for the fourth and fifth treatments remained the same as for the third treatment.

Epidermal cooling was achieved with the chiller tip set to maximum on the integrated cooling system. In addition, all treated areas were covered generously with clear contact cooling gel (Lumenis, Inc) before treatment.

Each patient received a total of 5 full-face treatments with the IPL device, spaced 3 weeks between treatments. Before each of the first 3 IPL treatments, half of each of the patients’ faces was treated with topical 5-ALA solution applied to the randomly assigned side. The last 2 treatments consisted of IPL only. A portion of a commercially available 5-ALA solution (Levulan Kerastick) was applied following a full-face acetone scrub and was left on for 30 to 60 minutes. The incubation time for the initial treatments was shorter, but it was lengthened according to the subject’s tolerability to the preceding treatment for the second and third treatments. The solution was applied in 2 coats to half of the face. The face was washed with a mild facial cleanser and water before the IPL treatments. Following IPL treatment, the patients washed their faces again and applied a facial moisturizer with sunscreen (Neutrogena Healthy Defense SPF [sun protection factor] 30 Daily Moisturizer; Neutrogena Corporation, Los Angeles, Calif). The patients received education and reminders regarding strict sun avoidance and sun protection following each treatment.

### PHOTODAMAGE VARIABLES

The photodamage variables evaluated in the study included fine lines, mottled pigmentation, tactile roughness, and sallowness; there was also a global score for photaging. These scores were recorded for each side of the face by an independent investigator (J.S.D.) before each treatment and 4 weeks after the final treatment, for a total of 180 patient visits. Each photodamage score was recorded on a 5-point scale (0-4). The scale for each variable was defined as follows.

**Global Score for Photaging**

For this variable, 0 indicates that facial skin is smooth to the touch, without significant fine lines or unevenness in pigmentation in any areas (cheeks, forehead, and the perioral area); 1, facial skin shows 1 area (cheeks, forehead, or the perioral area) of significant roughness, dyspigmentation (hypopigmentation or hyperpigmentation), or fine lines; 2, facial skin shows 2 areas of significant roughness, dyspigmentation, or fine lines or shows roughness, dyspigmentation, and fine lines in 1 area; 3, facial skin shows 3 areas with significant roughness, dyspigmentation, or fine lines or shows roughness, dyspigmentation, and fine lines in 2 areas; and 4, facial skin shows any degree of photodamage greater than 3.

**Fine Lines**

For fine lines, 0 indicates no evidence of fine lines; 1, rare fine lines that are widely spaced; 2, several discrete fine lines; 3, moderate number of fine lines in close proximity; and 4, many fine lines, densely packed.

**Mottled Pigmentation**

For this variable, 0 indicates evenly pigmented skin; 1, light hypopigmentation or hyperpigmentation involving small areas; 2, moderate hypopigmentation or hyperpigmentation involving small areas or light hypopigmentation or hyperpigmentation involving moderate areas; 3, moderate hypopigmentation or hyperpigmentation involving moderate areas, light hypopigmentation or hyperpigmentation involving large areas, or small areas of heavy hypopigmentation or hyperpigmentation; and 4, marked hypopigmentation or hyperpigmentation.

**Tactile Roughness**

For tactile roughness, 0 indicates that skin is smooth; 1, skin is smooth, with occasional rough areas; 2, mild roughness; 3, moderate roughness; and 4, severe roughness.

**Sallowness**

For this variable, 0 indicates that skin is pink; 1, skin is pale; 2, skin has a slight suggestion of yellowness; 3, skin is pale, with a moderate suggestion of yellowness; and 4, skin is pale, with a distinct suggestion of yellowness.

### PATIENT SATISFACTION SCORES AND BLINDED INVESTIGATOR EVALUATIONS

At visit 9, subjects completed an evaluation form assessing their satisfaction with the treatment on each side of the face and answered questions regarding the acceptability of treatment. They rated the results of each side of the face as excellent (very satisfied), good (moderately satisfied), fair (slightly satisfied), or poor (not satisfied at all). At visit 9, the blinded investigator also completed a cosmetic evalua-
tion on each side of the face, rating the improvement from baseline as excellent, good, fair, or poor.

The data obtained from the blinded investigator’s assessments and the patients’ assessments were entered into a spreadsheet (Microsoft Excel; Microsoft, Redmond, Wash). The treatment outcome for each of the photodamage variables was labeled improved if there was a decrease in score from baseline of at least 1 grade, and was labeled a success if the variable received a severity score of 0 or 1. Comparisons of 5-ALA followed by IPL and IPL alone were conducted using Cochran-Mantel-Haenszel tests, using SAS statistical software, version 9.1.3 (SAS Institute Inc, Cary, NC), stratified on subject. The Cochran-Mantel-Haenszel test stratified on subject using modified ridit scores was used to test for mean score differences between 5-ALA plus IPL and IPL alone with respect to investigator cosmetic evaluation and subject satisfaction scores.

TOLERABILITY ASSESSMENT

Tolerability assessments were performed by the unblinded investigator for each side of the face at every visit. Erythema, scaling and dryness, edema, and oozing/crusting/vesiculation were recorded on a 5-point scale from 0 (none) to 4 (severe). Stinging/burning was evaluated on a 4-point scale from 0 (none) to 3 (severe). Results from the analysis of the 48-hour tolerability assessments were analyzed using the Fisher exact test (2-sided P value). Each variable was dichotomized for analysis as absent or present with the exception of erythema (none and minimal or mild and moderate).

RESULTS

All 20 volunteers completed the study and all follow-up visits. Pretreatment with 5-ALA resulted in greater improvement in the photodamage variables compared with IPL alone with respect to the global score for photoaging, mottled pigmentation, and fine lines (Table).

GLOBAL SCORE FOR PHOTOAGING

More individuals experienced an improved score of at least 1 grade compared with baseline in the 5-ALA followed by IPL-treated side compared with the IPL-alone side after the third, fourth, and fifth treatments. More successful results (defined as a final score of 0 or 1) were achieved on the 5-ALA plus IPL–treated side compared with the IPL-only side after the fourth treatment.

MOTTLED PIGMENTATION

For mottled pigmentation, both groups improved over baseline. After the fourth treatment, there was more improvement in the 5-ALA plus IPL–treated side compared with the IPL-only side. This difference persisted after the fifth treatment. More successful results were also achieved after the fourth treatment on the 5-ALA plus IPL–treated side compared with the IPL-only side, which persisted after the fifth treatment.

FINE LINES

For fine lines, both treatment sides resulted in fewer fine lines, although there was no statistically significant improvement between treated sides, based on similar rates of improvement of at least 1 grade from baseline. For successful treatments for fine lines (defined as a final score

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Abbreviations: 5-ALA, 5-aminolevulinic acid; IPL, intense pulsed light; NS, not significant.

*Data are given as number (percentage) of subjects unless otherwise indicated. Values in bold indicate significance.
of 0 or 1), the 5-ALA plus IPL sides had more low scores after the fourth and fifth treatments than the sides treated with IPL alone.

TACTILE ROUGHNESS AND SALLOWNESS

While there was noticeable improvement over baseline scores for tactile roughness and sallowness, pretreatment with 5-ALA did not seem to enhance the results of the IPL treatment. However, there was not much room for further enhancement in tactile roughness and sallowness. Of both treatment groups, 16 (80%) to 17 (85%) had a score of 0 for tactile roughness (skin is smooth) at the end of the study.

SUBJECT SATISFACTION AND INVESTIGATOR COSMETIC EVALUATIONS

Subject satisfaction scores (Figure 1) and the final investigator cosmetic evaluations (Figure 2) were significantly better for the 5-ALA plus IPL–treated sides than the IPL-only–treated sides. With respect to the investigators’ cosmetic evaluation, 19 (95%) of the 5-ALA plus IPL–treated sides were rated as good or excellent, while only 12 (60%) of the IPL-only sides were rated as good and 0 were rated as excellent. The subject satisfaction scores demonstrated that 17 (95%) of the 5-ALA plus IPL–treated sides were rated as good or excellent, while only 14 (70%) of the IPL-only sides were in those categories. Both treatments were well tolerated, with no difference in the incidence or profile of adverse effects with or without 5-ALA pretreatment.

TOLERABILITY-ASSOCIATED ADVERSE EFFECTS

Erythema

Of the 20 subjects, 18 (90%) presented at baseline with some degree of erythema. Most (16 [80%]) had minimal or mild (grade 1 or 2) erythema at baseline. No point during the study was a subject recorded as having severe erythema. Forty-eight hours following the first treatment, the 5-ALA plus IPL–treated sides had more intense erythema than the IPL-only sides (10 [50%] vs 3 [15%]; \(P = .04\)).

Three weeks following the first treatment, both treatment sides had similar proportions of intensity of erythema. Repeat treatments did not seem to result in a more severe reaction than seen after the first treatment. Both treatment sides had 18 (90%) of the areas without erythema 4 weeks following the fifth treatment. This is in contrast to 18 (90%) of the subjects having at least minimal erythema at baseline.

Scaling and Dryness

Minimal or mild scaling and dryness was observed in 12 (60%) of the subjects at baseline. Forty-eight hours following the first treatment, the 5-ALA plus IPL–treated sides had more scaling and dryness than the IPL-only sides (10 [50%] vs 3 [15%]; \(P = .04\)). Similar patterns of scaling and dryness were seen in both groups at the remaining visits. At the final visit, almost all of the treated sides had no scaling and dryness present.

Edema

Only 1 subject presented with edema (minimal) at baseline. Forty-eight hours following the first treatment, the 5-ALA plus IPL–treated sides had more edema than the IPL-only sides (10 [50%] vs 2 [10%]; \(P = .01\)). The incidence of edema was low at the remaining visits, with no edema reported in either group following the third treatment.

Oozing/Crusting/Vesiculation

The incidence of oozing/crusting-vesiculation was low, with 4 (20%) of the 5-ALA plus IPL–treated sides having minimal or mild severity at 48 hours and at 1 week following the second treatment (\(P = .11\)). Oozing/crusting-vesiculation occurred once in 1 subject on the IPL-only side, 1 week following the second treatment. None of the treated sides had oozing/crusting-vesiculation following the fourth treatment.
Stinging and Burning

The only reported occurrences of stinging and burning on either treatment side were 48 hours following the initial treatment. The intensity of stinging and burning on the 5-ALA plus IPL–treated sides was minimal in 3 (15%) subjects and moderate in 1 (5%) subject. The IPL-only sides had minimal stinging and burning in 3 (15%) subjects; these were the same patients as those with stinging and burning on the 5-ALA plus IPL–treated sides.

Nonablative laser and light sources have been widely used for the reduction of the visible signs of photoaging for at least the past 5 years. The benefits of nonablative treatment include quicker patient recovery time because of the absence of marked postoperative erythema, desquamation, and crusting. Moreover, the risks of unwanted pigmented and textural abnormalities are much decreased in nonablative treatment compared with ablative treatment. The benefits of nonablative treatment are partially counterbalanced by its reduced efficacy relative to laser resurfacing. Among the novel methods for maximizing the efficacy of nonablative treatment is the concurrent use of a photosensitizing agent, such as 5-ALA.

Originally developed to be used with red or blue light to treat superficial cutaneous malignancies and premalignant lesions (eg, actinic keratoses), 5-ALA has more recently been used in combination with diverse light sources to increase the effectiveness of nonablative laser therapy. This cosmetic use entails shorter 5-ALA pretreatment regimens and less intense light fluences for activating the photosensitizer. Many of the methods by which 5-ALA and light are used to improve photodamage were first pioneered in the treatment of actinic keratoses and then applied to photodamage in the absence of frank precancers.

This so-called photodynamic photorejuvenation was discussed in the literature as early as 2002 when Ruiz-Rodriguez and colleagues treated 17 patients with a combination of actinic keratoses and diffuse photodamage. They applied 20% 5-ALA mixed in an oil-in-water emulsion and under occlusion for 4 hours before treatment (0.2 g/cm²) with the pulsed-light device (Lumenis, Inc), using a 615-nm cutoff filter and a total fluence of 40 J/cm² in a double-pulse mode of 4.0 milliseconds, with a 20-millisecond interpulse delay. Approximately three fourths of the actinic keratoses and adjacent photodamaged skin resolved 1 month after the first treatments, but posttreatment erythema, edema, and crusting lasted up to 10 days.

These results were extended by Alexiades-Armenakas and Geronemus, who showed that photodynamic treatment of actinic keratoses could be accomplished not only with IPL but also with a 595-nm pulsed-dye laser (PDL) (Vbeam; Candela Corporation, Wayland, Mass). The PDL offered the benefits of rapidity of treatment and the comfort and protective epidermal effects associated with cryogen spray cooling. The 5-ALA incubation times were as brief as 3 hours, and nonpurpuric PDL settings (4.0-7.5 J/cm²; pulse duration, 10 milliseconds; 10-mm spot size; and 30-millisecond cryogen spray with a 30-millisecond delay) were used. Minimal intraoperative stinging, burning, and pain were reported, and while there was some postoperative erythema, no purpura, crusting, or scarring was seen. While Alexiades-Armenakas and Geronemus were focused on the treatment of actinic keratoses, they demonstrated that 5-ALA could be effectively used with the PDL with little downtime.

Anecdotal use of IPL and PDL for improvement of the visible signs of skin aging has rapidly spread. Initial studies of this application are being published. Avram and Goldman retrospectively evaluated 17 patients treated with 5-ALA plus IPL, and found 55% improvement in telangiectasia, 48% improvement in pigmented abnormalities, and 25% improvement in coarseness of skin texture, but minimal change in fine wrinkles. Low doses of 5-ALA plus IPL permitted postoperative courses significant for mild erythema and edema for 3 to 5 days. Other preliminary studies have also indicated treatment efficacy following shorter contact time (30 minutes-1 hour) full-face incubation with 20% 5-ALA followed by treatment with IPL.

In the present, controlled, split-face study, the 5-ALA plus IPL–treated sides were associated with greater improvement on the various subscales compared with the IPL-only treated sides. The greatest relative improvements in the 5-ALA plus IPL–treated sides were in mottled hyperpigmentation and global photaging, and to a slightly lesser extent, in fine lines. Tactile roughness and sallowness also improved, but to no greater extent with 5-ALA pretreatment than with IPL alone. The blinded investigator and patients preferred the combined 5-ALA plus IPL treatment. This subjective analysis cannot be blinded because the subjects would recall having the solution applied to one side of the face.

To our surprise, adverse effects and tolerability did not differ significantly between the IPL-only treated areas and the areas treated with 5-ALA plus IPL. Reported adverse effects included erythema, purpura, and edema. Most resolved within 1 to 2 days, with the longest adverse effect lasting 5 days. Most were treated with cool compresses and oral nonsteroidal anti-inflammatory medication. None required corticosteroids. Of the 7 patients reporting adverse effects, 5 reported them as bilateral and 2 reported increased severity on the side treated with 5-ALA. There was no statistical difference in adverse effects between the 2 treated sides. In all prior studies, use of ALA with virtually any light source caused at least some discomfort, redness, swelling, and crusting. This is likely attributed to the strict sun avoidance practiced by study volunteers for the rest of the day after treatment and the following few days. Volunteers stayed inside, away from windows and indirect sunlight, and used a moisturizer with a sun protection factor of 30. For any situations in which they had to go outside, they donned sun protection in the form of hats and scarves in addition to sunscreen. In the clinical nonresearch setting, phototoxicity would be expected at least to some extent in patients...
undergoing 5-ALA pretreatment with IPL. Careful patient selection, patient education, and careful sun avoidance for up to 36 hours after treatment will be essential to successful 5-ALA plus IPL treatments.

The benefits of the addition of 5-ALA to IPL treatments demonstrated in this study are greater improvement of photoaging and specifically of dyspigmentation and fine wrinkles with the same number of treatments. While we did not specifically assess whether the addition of 5-ALA produced more improvement vs IPL alone per treatment, it would seem from examining the patients and parsing the data that had the study been terminated after just 3 treatments, administering 5-ALA plus IPL to one side of the face and IPL alone to the other side, that an even greater difference would have been demonstrated.

Although telangiectasias and facial redness were not variables that were formally evaluated in this study, review of the prestudy and poststudy photographs revealed considerable improvement of telangiectasias and facial redness in the IPL alone and 5-ALA plus IPL–treated sides.

There are several potential downsides to the use of 5-ALA in the treatment of photoaging. Adding 5-ALA to IPL treatments increases the cost. Each application of 5-ALA adds approximately $100 to the cost of each treatment. While the drug is covered by many insurers when actinic keratoses are being treated, the cost of 5-ALA is not covered when photoaging is being treated in the absence of actinic keratoses. This additional cost will be paid for either by the physicians or most likely by the patient. If, however, further study confirms our suspicion that three 5-ALA plus IPL treatments produce the same results as 5 or 6 IPL treatments, then the patient will, in the end, benefit from the same results at a lower cost. The other concern is phototoxicity. Strict avoidance of sun and bright lights is essential to limit the redness, swelling, crusting, and pain associated with 5-ALA–induced phototoxicity. Some clinicians prefer that patients do not practice sun avoidance after these treatments with the yet unproved belief that obtaining uncontrolled light exposure after the treatment produces more vigorous phototoxicity, which yields better outcomes. If this approach is used, patients must be warned of expected adverse effects.

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