Safety and Cosmetic Effects of Photodynamic Therapy using Hexyl Aminolevulinate and Intense Pulsed Light

A Pilot Study Conducted in Subjects with Mild-to-moderate Facial Photodamage

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ABSTRACT

Objective: To assess the cosmetic effects of photodynamic therapy with hexyl aminolevulinate cream and intense pulsed light in subjects with mild-to-moderate facial photodamage. **Design:** Six-month, open-label, single-center, pilot study comprising three study treatments, each separated by 30 days, and two follow-up visits (one and four months following third treatment). **Setting:** Tennessee Clinical Research Center, Nashville, Tennessee. **Participants:** Ten women (ages 36 to 64 years) with skin color classified as Fitzpatrick I to III. **Measurements:** The investigator evaluated erythema, dryness, bruising, crusts and erosions, and stinging/burning immediately before and after each treatment and at each follow-up visit. In addition, the investigator rated cosmetic appearance at each follow-up visit. Subjects rated stinging, tingling, itching, and burning 15 minutes after each treatment and cosmetic effects (radiance, smoothness, pore appearance, evenness of skin tone, and overall effect) at each follow-up visit. **Results:** Mean (standard error of the mean) objective cosmetic appearance scores were 0.900 (0.233) and 1.400 (0.267) (0=very much improved; 1=much improved; 2=improved) one and four months following treatment, respectively. Mean subjective assessments of radiance, smoothness, pore appearance, evenness of skin tone, and overall effect ranged from 2.200 to 2.800 (2=much improved; 3=improved) one and four months following treatment. Mean objective erythema, dryness, bruising, and stinging/burning scores were <1 (minimal/slight) at all time points. Mean subjective post-treatment stinging, tingling, itching, and burning scores were <1 (mild) at all time points. **Conclusion:** Photodynamic therapy with hexyl aminolevulinate and intense pulsed light improved cosmetic appearance and was generally well tolerated. Further investigation in larger patient populations is warranted. (*J Clin Aesthet Dermatol.* 2013;6(10):27–31.)

Visible changes in skin appearance resulting from sun exposure (ultraviolet [UV] light) are common among adults and include sagging skin, wrinkles, and changes in skin color and texture.[1] Many adults with such photoaging seek the restoration of a more youthful appearance; therefore, there is a great demand for cosmetic procedures, particularly those that are noninvasive and well tolerated. Statistics compiled by the American Society of Plastic Surgeons indicate that more than 12.2 million minimally invasive cosmetic procedures were performed in the United States in 2011, predominantly botulinum toxin, dermal fillers, and laser hair removal.[2] Most of the reported procedures (10.7 million [88%]) were performed on women.[2]

Intense pulsed light (IPL) therapy is one of several nonsurgical procedures used for the treatment of facial

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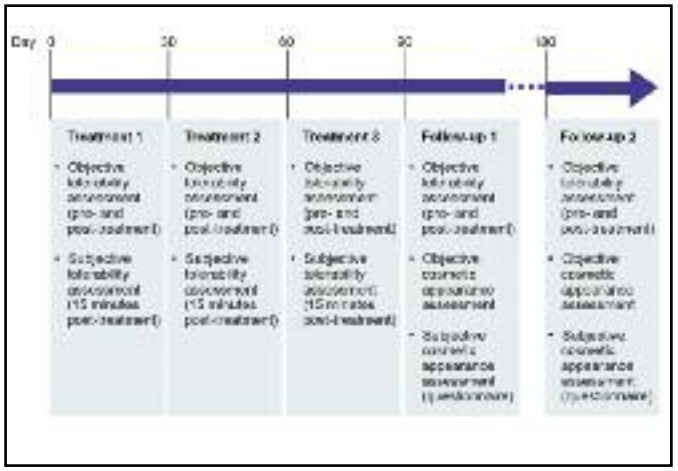

Figure 1. Study design

photodamage. IPL utilizes high-intensity (nonlaser) light sources to produce broad-spectrum light wavelength pulses over relatively large treatment areas.[3] Energy absorbed by chromophores in the dermis results in selective photothermolysis, sparing surrounding nonpigmented tissue. The utility of IPL for the treatment of photodamage was first established in 2000 in a study in which subjects who underwent four to six full-face IPL treatments (Vasculight, ESC/Sharplan, Norwood, Massachusetts; 500–1200nm wavelength and fluence of 30–50 J/cm^2) at three-week intervals demonstrated visible improvement in all aspects of photoaging, including fine wrinkles, irregular pigmentation, skin texture, pore size, and telangiectasias.[4] Since that time, numerous clinical studies have provided additional evidence of the beneficial effects of IPL on wrinkles, skin texture, telangiectasias, pigmentation, and collagen formation.[3,5–7] Observed beneficial effects in photodamaged skin are believed to reflect contracture of collagen fibers (improved skin texture), increased synthesis of extracellular matrix proteins (increased dermal volume), and increased collagen I, collagen III, and elastin synthesis.[3] Damage to nontargeted surrounding tissue is generally limited.[3]

Aminolevulinic acid (ALA) and methyl aminolevulinate (MAL) are topical photosensitizers that have been evaluated in combination with various light sources, including IPL.[8–13] Studies evaluating safety and efficacy of these agents in combination with blue or red light have demonstrated cosmetic benefits in subjects with photodamaged skin[8,10]; however, phototoxicity limits use in some patients.[8,10]

In several small split-face studies, the application of ALA prior to IPL therapy was associated with greater improvement in photodamage parameters (e.g., crow's feet, tactile skin roughness, mottled hyperpigmentation, telangiectasias, and actinic keratoses) compared with IPL alone, with minimal impact on tolerability.[11–13]

Hexyl aminolevulinate (HAL) is an ester of ALA that has demonstrated cosmetic benefits and minimal side effects when used in combination with red or blue light in adults with visible signs of aging and photodamage.[14,15] The objective of the current six-month pilot study was to assess the effects of photodynamic therapy with HAL and IPL in subjects with mild-to-moderate facial photodamage.

METHODS

Subjects. Adults between 30 and 65 years of age (mean [standard deviation, SD], 50.0 [8.2]) with Fitzpatrick skin types I, II, or III[16] and mild-to-moderate facial photodamage (grade 2–3, as determined by the investigator using a 5-point scale [0=none, 1=minimal, 2=mild, 3=moderate, 4=severe]) were eligible for participation in the study. Subjects of childbearing potential were required to use an accepted form of contraception.

Subjects were excluded from participation in the study if they were pregnant; presented with conditions, such as sunburn, rashes, scratches, or burn marks that could interfere with study evaluations; or had a history of allergies to cosmetics, toiletry products, or test materials. Exclusion criteria also included a history of migraine headaches; acute or chronic dermatologic, medical, and/or physical conditions that could interfere with treatment or influence the outcome of the study; use of medications or oral supplements that could influence the outcome of the study or interfere with observations (e.g., systemic or topical corticosteroids, anti-inflammatory drugs, antihistamines, or retinoids); use of antiaging products (e.g., hydroquinone) for three months prior to study participation; a history of botulinum toxin injections, facial peels, and/or laser treatments within six months of study initiation; and participation in a cosmetic study involving the face within one week of study initiation.

Study design. This was a six-month, open-label, single-center, pilot study comprising three study treatments, each separated by 30 days, and two follow-up visits (1 and 4 months following the final treatment) (Figure 1). Phone visits were also conducted three days after each treatment.

Intervention. Prior to treatment, subjects washed their faces with a nonmedicated soap (Cetaphil®, Galderma Laboratories), rinsed thoroughly with water, and dried their face gently with a clean towel or single-use paper towel. Study personnel then applied approximately 2g of cream containing HAL (Allumera®, Photocure, Princeton, New Jersey) to all areas of the subject's face, except those that would be covered with goggles during exposure to light. After one hour, subjects washed with the nonmedicated soap, rinsed, and dried their face.

The entire face was then exposed to IPL (Lumenis One™, Lumenis, Yokneam, Israel; 560nm wavelength, beam diameter of 15x35mm, and fluence of 13–18J/cm^2); changes in the IPL settings were permitted based on skin type, tolerability to treatment, and the investigator's overall assessment of the case. After treatment, subjects washed with nonmedicated soap, rinsed, and dried their face; applied moisturizer (Cetaphil® lotion); and applied sunscreen (minimum SPF 30). Subjects were instructed to avoid outdoor light for up to 48 hours, if possible, and to

TABLE 1. Intense pulsed light treatment parameters

SUBJECT	SPOT SIZE (mm)*	PULSE DURATION (ms)*	FLUENCE (J/cm²)		
			TREATMENT 1	TREATMENT 2	TREATMENT 3
1	15x35	4, 4 double 20ms delay	14	17	18
2	15x35	4, 4 double 20ms delay	14	16	17
3	15x35	3.5, 3.5 double 15ms delay	14	15	18
4	15x35	3.5, 3.5 double 15ms delay	14	17	18
5	15x35	3.5, 3.5 double 15ms delay	15	15	15
6	15x35	4, 4 double 20ms delay	14	16	18
7	15x35	4, 4 double 20ms delay	14	18	18
8	15x35	3.5, 3.5 double 15ms delay	17	18	18
9	15x35	3, 3 double 10ms delay	13	16	18
10	15x35	3.5, 3.5 double 15ms delay	14	16	18

Abbreviations: mm=millimeters; ms=milliseconds; J/cm²=joules per square cenitmeter
*For each subject, spot size and pulse duration remained the same for all three treatments.

wear light-protective clothing whenever outside during the first 48 hours after treatment (longer if prickling sensation upon outdoor light exposure beyond 48 hours).

Facial photographs (full face, and right and left 45° angles) were captured before and immediately after each treatment using the OMNIA Imaging System (Canfield Scientific, Inc., Fairfield, New Jersey).

Objective assessments. The investigator rated cosmetic appearance at each of the two follow-up visits using a 5-point scale (0=very much improved, 1=much improved, 2=improved, 3=no change, 4=worse).

The investigator evaluated local tolerability signs and symptoms immediately before and after each treatment and at each follow-up visit. Erythema, dryness, and bruising were each rated using a 5-point scale (0=absent, 1=slight, 2=mild, 3=moderate, 4=severe). Crusts and erosions were also rated using a 5-point scale (0=none, 1=rare [1–2 lesions; ≤3mm in size], 2=mild [3–5 lesions; ≤3mm in size, areas readily seen], 3=moderate [6–10 lesions; easily seen], 4=severe [>10 lesions]). Stinging/burning was rated using a 4-point scale (0=none, 1=minimal, 2=moderate, 3=severe; overall average impression related to level of discomfort since the last evaluation). Adverse events were monitored throughout the study.

Subjective assessments. Subjects rated cosmetic effects (radiance, smoothness, pore appearance, evenness of skin tone, and overall effect) at each follow-up visit (1=very much improved, 2=much improved, 3= improved,

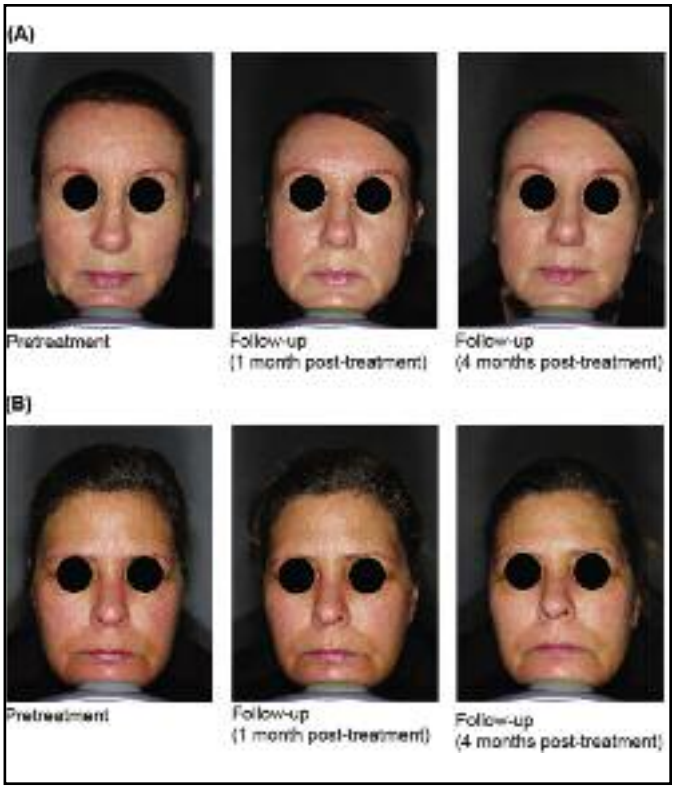

Figure 2. Clinical examples of cosmetic appearance in (A) a 48-year-old woman with Fitzpatrick skin type II and (B) a 47-year-old woman with Fitzpatrick skin type III. Photographs were taken before treatment and 1 and 4 months after treatment.

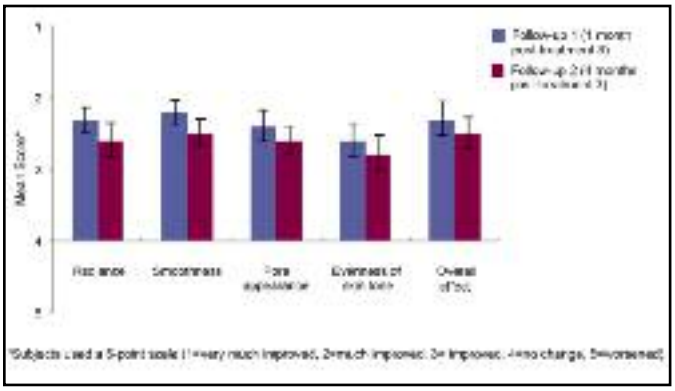

Figure 3. Mean subjective assessments of radiance, smoothness, pore appearance, evenness of skin tone, and overall effect at 1 and 4 months following the final treatment*

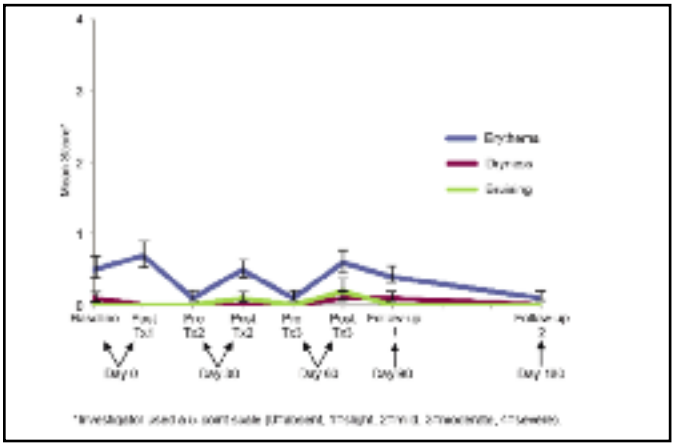

Figure 4. Mean (SEM) investigator rated erythema, dryness, and bruising throughout the study*

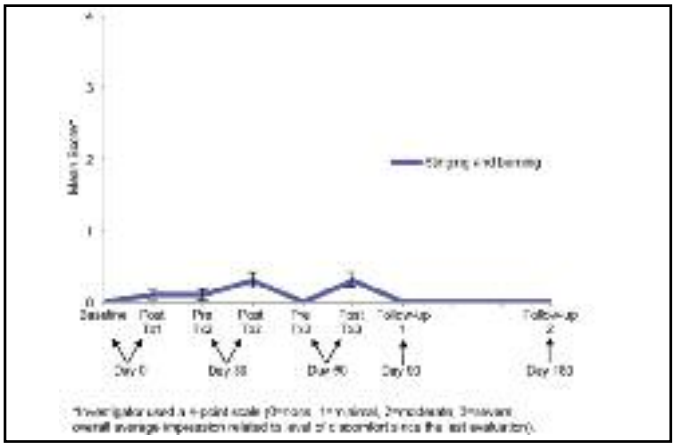

Figure 5. Mean (SEM) investigator rated stinging/burning throughout the study*

4=no change, 5=worsened) and stinging, tingling, itching, and burning 15 minutes after each treatment using a 4-point scale (0=none, 1=mild, 2=moderate, 3=severe).

RESULTS

Subjects (disposition/demographics). A total of 10 female subjects enrolled in and completed the study. Subjects ranged in age from 36 to 64 years. The majority had skin type II (n=5) or III (n=4). The IPL treatment parameters are summarized in Table 1.

Cosmetic effects. Objective assessments of cosmetic appearance were much improved at one and four months following the final treatment (mean [standard error of the mean, SEM] score, 0.900 [0.233] and 1.400 [0.267], respectively; 1=much improved; 2=improved). Clinical examples are shown in Figure 2.

Mean subjective assessments of radiance, smoothness, pore appearance, evenness of skin tone, and overall effect ranged from 2.200 to 2.800 (1=very much improved, 2=much improved, 3=improved, 4=no change, 5=worsened) at one and four months following the final treatment, indicating improvement in cosmetic appearance (Figure 3). Improvement was greater at the first assessment than at the last assessment, suggesting that additional treatments may be warranted.

Tolerability. Overall, minimal erythema, dryness, and bruising were observed by the investigator (Figure 4). Most subjects (8 of 10) experienced at least one episode of slight-to-mild erythema. Each of the three subjects who experienced dryness had one episode of slight dryness (baseline [n=1], post-treatment 3 [n=1], and one month after the final treatment [n=1]). Minimal bruising occurred throughout the study; however, none was reportable as an adverse event nor persisted, and no evidence remained at the end of the study. Minimal stinging/burning was observed during the study (Figure 5).

Subjective assessments of post-treatment stinging, tingling, itching, and burning were consistent with good tolerability. Mean scores at all time points were less than 1 (0=none, 1=mild, 2=moderate, 3=severe) (Table 2).

Adverse events. Crusts were observed in one subject following the first and second treatments. These resolved without intervention before the third treatment. No other cases were noted, and no evidence remained at the end of the study.

DISCUSSION

In this pilot study, photodynamic therapy with a HAL-containing cosmetic cream and IPL improved cosmetic appearance (investigator- and subject-rated) and was generally well tolerated. Overall, minimal erythema, dryness, bruising, and stinging/burning were observed. Only one subject experienced an adverse event (crusts following the first and second treatments, which resolved without intervention before the third treatment). These findings suggest that the combination of a HAL-containing cosmetic cream and IPL may be a useful, noninvasive, and well-tolerated cosmetic option for individuals seeking the restoration of a more youthful appearance.

Tolerability is an important aspect of any treatment for facial photodamage. Erythema, edema, and oozing/crusting/vesiculation have proven problematic in some studies of photodynamic therapy with an ALA-containing pharmaceutical and IPL, although reported rates were

TABLE 2. Mean (SEM) subjective ratings of stinging, tingling, itching, and burning 15 minutes after treatments 1, 2, and 3*

ASSESSMENT	TREATMENT 1	TREATMENT 2	TREATMENT 3
Stinging	0.444 (0.242)	0.600 (0.163)	0.500 (0.167)
Tingling	0.400 (0.163)	0.400 (0.163)	0.200 (0.133)
Itching	0.100 (0.100)	0.100 (0.100)	0.100 (0.100)
Burning	0.300 (0.213)	0.300 (0.153)	0.400 (0.221)

Subjects used a 4-point scale (0=none, 1=mild, 2=moderate, 3=severe)

highly variable: rates of erythema range from <10 to 100 percent, rates of edema range from 9 to 100 percent, and rates of oozing/crusting/vesiculation range from 20 to 100 percent.[11–13] Postinflammatory hyperpigmentation was described as the most severe side effect in one small split-face study conducted in Chinese patients with Fitzpatrick skin types III and IV (N=26), with reported incidences of 22 and 15 percent on the ALA/IPL side and IPL-only side, respectively.[13]

Whereas the current study provides evidence of the cosmetic potential of photodynamic therapy with HAL and IPL in subjects with mild-to-moderate facial photodamage, interpretation of these results is limited by the small sample size and open-label, noncomparative study design. Additional larger, comparative studies are needed to confirm these initial promising findings.

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