

Original
Article

Intense Pulsed Light alone versus Intense Pulsed Light and aminolevulinic acid in the treatment of photodamaged skin: importance of long term follow-up

ABSTRACT

Introduction: Intense pulsed light (IPL) is an option in the treatment of photoaging. When combined with photodynamic therapy (PDT), using 5-aminolevulinic acid (ALA), it has become a tool of great interest in the treatment of photodamaged skin with actinic keratoses (AKs). **Objective:** Determine the long-term efficacy of the treatment of photodamaged skin with actinic keratoses using the combination ALA-IPL, and compare the treatment of photodamaged skin using ALA-IPL and IPL alone. **Material and methods:** Nine patients with photodamaged skin underwent two sessions, with a month interval, of ALA-IPL on one hemiface and IPL alone on the contralateral side of the face. Follow-up lasted 12 months. **Results:** AK lesions clearance was observed only on the area treated with 5-ALA+IPL (62,9%) after 3 months of follow up. Recurrence of the improved lesions (70,6%) was observed in 12 month follow up. Improvement of melanoses, telangiectasia and wrinkles were observed on both sides, but more evident on the side treated with 5-ALA+IPL. **Conclusion:** The association of ALA-IPL treatment improves overall photodamaged skin, including the treatment of actinic keratoses, which does not occur without the association of ALA. Long term follow-up of keratoses healing rate is necessary to evaluate the treatment efficacy.

Keywords: photodynamic therapy, aminolevulinic acid, rejuvenation.

INTRODUCTION

Several types of laser or intense pulsed light (IPL) have been currently used for facial rejuvenation.

Some signs of photoaging, such as changes in skin texture, fine wrinkles, melanosis and telangiectasias, are treated effectively and safely by IPL.^{1,2,3} However, the actinic keratoses (AKs) do not respond to this therapy alone.

Photodynamic therapy (PDT) is a new method for treating skin lesions, which associates photosensitizing substances and light sources. An example is the association of topical 5-aminolevulinic acid (ALA) 20% with IPL (ALA-IPL), which seems to be a promising treatment for photodamaged skin with AKs.^{4,5,6} ALA can be applied to isolated lesions or over the total area of treatment.⁷ Some authors consider PDT a good alternative to conventional treatments, such as the use of topical 5-fluorouracil (5 - FU).⁸ Topical PDT, using ALA associated with blue light and methyl-aminolevulinate (MAL) associated with red light, is an established treatment for AKs. MAL, a photosensitizer also approved for topical PDT in several countries, including Brazil, is a modified molecule of ALA and has proved to be effective for treating not only AKs but also for some types of basal cell carcinomas. Treatment of Bowen's disease with this method is still not approved in Brazil, although it is already used in several countries of the world.^{9,10,11}

Different protocols are reported for the treatment of photodamaged skin using ALA-PDT. Some authors suggest the use of ALA with a short incubation period, and report that the

Authors:

Maria Cláudia Almeida Issa¹
Carlos Barcauí²
Alexandra Cariello Mesquita³
Fernanda Ramos Franco de Sá⁴
Mônica Manela-Azulay⁵

¹Assistant Doctor of Dermatology Service, Universidade Federal Fluminense (UFF) and PhD in Dermatology, Universidade Federal do Rio de Janeiro (UFRJ)

²PhD in Dermatology, Universidade de São Paulo (USP)

³Postgraduate student, Universidade Federal Fluminense (UFF)

⁴Postgraduate student, Universidade Federal Fluminense (UFF)

⁵PhD in Dermatology, Universidade Federal do Rio de Janeiro (UFRJ)

Correspondence to:

Maria Cláudia Almeida Issa
Praia de Icaraí, 139 - 702,
Icaraí, Niterói - Rio de Janeiro
CEP: 24230-001
Phone: +55 (21) 2620-7162 /
+55 (21) 2704-1680
E-mail: mariaclaudia@predialnet.com.br

Submitted on: 06/20/2009

Approved on: 09/10/2009

We declare no conflict of interest.

time reduction does not alter the treatment efficacy.¹² So far, there is no single protocol for topical PDT in the treatment of photoaging. A recent study on clinical, histological and immunohistochemical changes induced by MAL-PDT in 14 patients with photodamaged skin, with and without actinic keratoses, was reported by Issa *et al.*¹³ The authors found an increase of collagen and a decrease of elastic fibers statistically significant after two sessions of MAL and red light. Histopathological findings corroborated the clinical improvement found, which occurred in the photodamaged skin, even without evident actinic keratosis clinical lesion.

This study aims to evaluate the efficacy of ALA topical application followed by IPL irradiation in the treatment of AKs with long-term follow-up and to identify the degree of global improvement of photodamaged skin by this method.

MATERIAL AND METHODS

The study group consisted of 9 outpatients from the Dermatology Department of the *Hospital Universitário Antônio Pedro, Universidade Federal Fluminense (HUAP/UFF)*, aged from 41 to 83 years, with signs of photoaging, including wrinkles, rough skin, hyperpigmentation, telangiectasias, and three or more AK lesions on the face. Eight patients were female and one, male. All had Fitzpatrick's skin phototypes II-III and degree of photoaging III by the classification of Glogau. None had been previously submitted to PDT. All AKs had been treated with other methods such as topic 5-fluorouracil, chemical cauterization with trichloroacetic acid 35%, electrocoagulation or excision, for a period of six months or more before the study. Patients were instructed to use only sunscreen lotion with sun protection factor (SPF) 30, and to avoid sun exposure during the entire period of the study follow-up.

Exclusion criteria were the presence of pregnancy, lactation, collagen diseases, porphyria, or any topical treatment for at least four weeks prior to the start of the study. After appropriate explanations, all patients signed an informed consent form, with detailed information about the treatment.

Patients were followed-up by two dermatologists during the study period. Photographic evaluation was conducted by the physician (camera type: Sony Cyber-shot 5.0 mega pixels) at the Dermatology ambulatory of HUAP. Evaluation criteria included clinical improvement in texture, wrinkles depth, decreased pigmentation, and telangiectasia of the actinic keratosis lesions after 3, 6 and 12 months of treatment. The improvement degree of the variable textures, wrinkles, pigmentation, and telangiectasia was evaluated subjectively using a scale described by Alster *et al.*¹⁴ in a study that evaluated the efficacy of PDT in photodamaged skin. This scale considers minimal improvement (< 25%), moderate (25% -50%),

significant (51-75%), and excellent (> 75%). The variable AK was evaluated objectively by numerical quantification. Side effects such as erythema, edema, and desquamation were evaluated by medical observers. The scale used had a numerical value of 0 to 10, and defined as mild (1 to 3), moderate (4 to 6), and intense (greater than 7). Pain was rated subjectively by patients using the same scale.

In this study, the photosensitizer used was aminolevulinic acid. ALA powder to prepare the cream was manufactured in Germany (Chemos®), and was compounded in a 20% cream.

Technique: In a place protected from ambient light, a uniform layer of approximately 1 mm thick of ALA was applied in all patients without occlusion in the hemiface with the largest number of AKs, for a period of 2 hours. Topical anesthetics were not used. Before IPL application, we observed the red-orange fluorescence of AKs through the light of Wood's lamp. After ALA removal with gauze and saline 0.9%, the whole face was covered with a layer of 2 to 3 mm of ultrasound gel (RMC®), as a preparation for IPL application. The IPL equipment used was Vasculight Plus®, and was used a filter of 615 nm, fluency of 40 J/cm², two pulses of 20 ms. The sessions were performed with a single pass in the face. A second shot of IPL was performed only on AK lesions.

Patients received two treatments with one month interval. It has been prescribed oral analgesic (paracetamol) for some patients who did not tolerate pain. We did not use topical or oral corticosteroid therapy in any case. Patients were instructed to use sunscreen and avoid sun exposure for 48 hours after each session. After this period, they were allowed to perform their routine activities using sunscreen and corrective foundation. All sessions of ALA-PDT were performed in private clinics, and patients were followed in the Dermatology ambulatory of HUAP and in the private clinics after 48 hours, 7 and 15 days of the PDT session during the first two months. The evaluations were carried out after 3, 6, and at the end of 12 months.

RESULTS

The nine patients included completed the study. They were classified as skin phototypes II and III, having photoaging type III according to Glogau's scale, with a mean age of 61.3 years.

According to clinical evaluation and photography, after the third month of treatment, there was improvement of AKs only in the hemiface treated with ALA-IPL, with a decrease in their numbers. The total number of AK lesions among all patients before treatment was 54, which decreased to 34 after three months of treatment, with complete remission in 62.9%. Some patients had partial improvement of some AK lesions and cure of other (Figure 1). After six months of treatment, remission of AK lesions was maintained; however, after 12

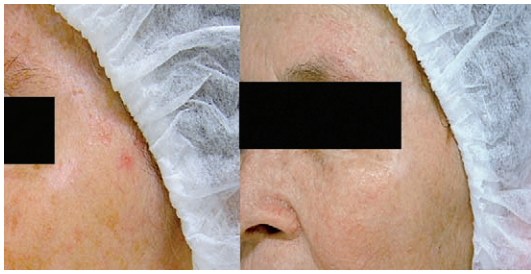


Figura 1 – Cura completa das lesões de ceratoses actínicas no lado tratado com ALA-LIP após três meses de tratamento.

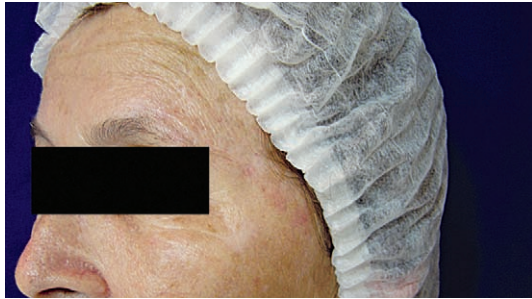


Figura 2 – Recorrência das lesões de ceratoses actínicas na região temporal esquerda tratada com ALA-LIP após 12 meses de tratamento.

months, the relapse rate was 70.6% (Figure 2). There was no change in appearance or number of lesions on the side treated with IPL alone.

With regard to other signs of photoaging, we observed clinical improvement on both sides treated with ALA-IPL and IPL alone after three months of treatment. All patients showed overall clinical improvement in variable degrees (texture, wrinkles, pigmentation, and telangiectasia). According to the scale used in this study, after treatment with ALA-IPL, we observed: minimal improvement in fine wrinkles, moderate improvement in texture, telangiectasias and melanosis after three months (Figure 3). In the sixth month, the improvement achieved in the third month was maintained, and, at the end of 12 months, this improvement was not observed. In the hemiface treated only with IPL, there was minimal improvement of texture and fine wrinkles, and



Figura 3 – Melhora clínica global de todos os aspectos do fotoenvelhecimento no lado tratado com ALA-LIP após três meses de tratamento.

mild improvement of telangiectasia and melanosis after three months. The improvement was maintained until the sixth month of treatment, and no longer observed at the end of 12 months (Table 1).

Side effects such as erythema, edema and desquamation were evaluated by the physicians, and patients and physicians agreed in their evaluations of the side effects. Erythema and edema were observed between 24 and 48 hours, and scaling, in the period from 7 to 10 days. They were classified, according to the scale used in the study, as mild to moderate in eight patients and as intense in one patient who exposed her face to sunlight 24 hours after the first session, disobeying medical instructions (Figure 4). Burning pain, reported by all patients, was considered mild. This discomfort occurred during the sessions and after the period immediately after treatment, with a gradual decrease in the subsequent 48 hours.

DISCUSSION

ALA is a precursor of protoporphyrin IX (PpIX) in the biosynthetic pathway of heme. ALA penetrates mainly the epidermis of lesions such as AKs and is enzymatically converted into protoporphyrin. The PpIX, when illuminated by a light source with an appropriate wavelength, triggers a phototoxic reaction followed by free radicals production, leading to destruction of malignant cells.⁹ There are different sources of light that can be used in PDT with different wavelengths. PpIX has an absorption peak between 410 and 630 nm.⁵ Different light sources have different physical characteristics, wavelength, fluency, type and duration of pulse. Thus, the energy emitted, time of light exposure, intensity of light absorption by PpIX, and the light penetration depth into the skin are important factors for the outcome of PDT. There are several sources of light used for treatment with ALA-PDT, including the broad-spectrum light that is neither coherent nor collimated, such as IPL and the blue or red visible light. IPL is reported in several studies as a source of light for PDT in skin rejuvenation treatments.^{6,9,10}



Figura 4 – a) Paciente apresentando eritema e edema após 48 horas do tratamento com ALA-LIP e b) descamação após sete dias do tratamento com ALA-LIP.

Tabela 1 – Comparison of the clinical improvement degree during both treatment phases

	ALA-IPL			IPL alone		
	After 3 months	After 6 months	After 12 months	After 3 months	After 6 months	After 12 months
Actinic keratoses	62.9%	Maintained	29.4%	No improvement	No improvement	No improvement
Texture	Moderate	Moderate	Improvement no longer observed	Minimal	Minimal	Improvement no longer observed
Telangiectasias	Moderate	Moderate	Improvement no longer observed	Moderate	Moderate	Improvement no longer observed
Melanosis	Moderate	Moderate	Improvement no longer observed	Moderate	Moderate	Improvement no longer observed
Fine wrinkles	Minimal	Minimal	Improvement no longer observed	Minimal	Minimal	Melhora Não Mais Observada
Minimal (< 25%); Moderate (25% a 50%); significant (51% a 75%); Excellent (> 75%).						

The innumerable studies that prove the efficacy of PDT in the treatment of AKs, using ALA as a photosensitizer and IPL as a light source, were carried out with different techniques, varying in the preparation (with or without ALA occlusion) and in the incubation time of this photosensitizer. Factors such as ALA incubation time, prior curettage, occlusion of the lesion to be treated, and source of light used are variables that can completely change the final outcome of PDT. Such differences in technique make it difficult to evaluate its efficacy. Furthermore, studies report efficacy after a short evaluation period, not reporting the possible recurrences after an extended follow-up. Our study draws attention to the evaluation of these criteria, by showing that it is extremely important to compare results when the technique used is the same. Besides the source of light, the photosensitizer chosen may change the treatment efficacy of topical PDT.

Alster *et al.*¹⁴ conducted a study with a similar design to ours, comparing the two treatments, one on each side of the face. Ten patients with mild to moderate degree of photoaging signs underwent two sessions of ALA-IPL, with an incubation period of 1 hour, four weeks apart. The results also showed more significant improvement on the side treated with ALA, compared to IPL alone, and the study had a six months of follow-up after the last treatment session. This is a follow up period shorter than the one used in the present study.

Avram and Goldman,¹ using 1 hour to prepare the skin with ALA, followed by the application of IPL in 17 patients, reported 68% of AKs clearance, as well as 55% improvement in telangiectasias, 48% in pigmentation, and 25 % in skin texture after a single session. The results of this study showed overall clinical improvement and AK lesions healing rate very close to those in the present study. Ruiz-Rodriguez *et al.*,⁵ in 2002, reported the use of ALA 20% on AK and IPL (615 nm filter) with 4 hours of incubation period, to treat 17 patients with photodamaged skin. Patients received two treatments with one month interval. Thirty-three of the 38 AK lesions (91%) were considered resolved after three months follow-up.

Although the results reported by all these authors show treatment efficacy of photodamage signs with ALA-

IPL, relapse rate after a long period of follow-up was not mentioned, revealing the clinical changes achieved in a period between 3 and 6 months after treatment.

Our primary results confirm the results reported by other authors. However, we used compounded ALA, and we must remember that the possible differences in the properties of compounded and industrialized photosensitizers may have contributed to the observation of recurrence when performed by a longer follow-up period. This differs from the world literature in which most studies with ALA-PDT uses industrialized ALA, and opens a bias in the evaluation of this treatment efficacy.

CONCLUSION

Based on the methodology and sample size in this study, PDT with ALA-IPL and IPL alone showed global improvement of some aspects of skin photoaging, such as texture, pigmentation, telangiectasias, and fine wrinkles. The association of topical photosensitizer also allows the treatment of AK lesions. The results achieved with ALA-IPL were better when compared to those found with the use of IPL alone.

Our results corroborate those reported by literature, where the use of topical ALA 20% followed by IPL shows to be a practical therapeutic method in the management of several clinical aspects of photoaging. Clinical improvement is evident as early as two weeks after the sessions, and the side effects are well tolerated by the patients. Compared to other methods used in AK treatments, such as 5-fluorouracil 5%, cryotherapy, electrocoagulation and surgery, PDT using ALA-IPL shows faster clinical results and less morbidity.

The association of photosensitizer with IPL allows the treatment of all the photodamage components. Its efficacy in the treatment of AK lesions makes the method a safe and effective option. However, the assessment of efficacy in a short period of time, after three months of treatment, as in most reported series, may not adequately represent the true healing rate of AK lesions with this method. IPL as light source can not trigger a photochemical reaction in an ideal way to produce cytotoxic radicals in sufficient quantity to promote

the effective destruction of all premalignant cells. Thus, it would not prevent the development of subclinical AK lesions, leading to a relapse after a longer period of follow-up. The follow-up of our patients, for a period longer than six months, showed a higher recurrence rate compared to those reported in the literature, which makes us suggest the importance of a long term follow-up in AK treatment with ALA-IPL.

REFERENCES

1. Bitter PH. Noninvasive rejuvenation of photodamaged skin using serial, full-face intense pulsed light treatments. *Dermatol Surg* 2000;26(9):835-842, discussion 843.
2. Goldgerg DJ, Cutler K B. Nonablative treatment of rhytids with intense pulsed light. *Lasers Surg Med* 2000;26(2):196-200.
3. Weiss RA, Weiss MA, Beasley KL. Rejuvenation of photoaged skin: 5 years results with intense pulsed light of the face, neck and chest. *Dermatol Surg* 2002;28(12):1115-1119.
4. Avram DK, Goldman MP. Effectiveness and safety of ALA-IPL in treating actinic keratoses and photodamage. *J Drugs Dermatol* 2004;3(Suppl 1):S36-9.
5. Ruiz-Rodriguez R, Sanz-Sánchez T, Córdoba S. Photodynamic Photorejuvenation. *Dermatol Surg* 2002; 28(8):742-744, discussion 744.
6. Piacquadro D, Chen D, Farber H et al. Photodynamic therapy with aminolevulinic acid topical solution and visible blue light in the treatment of multiple actinic keratoses of the face and scalp: investigator-blinded, phase 3, multicenter trials. *Arch Dermatol* 2004;140(1):41-6.
7. Goldman M, Atkin D. ALA/PDT in the treatment of actinic keratosis: spot versus confluent therapy. *J Cosmet Laser Ther* 2003;5(2):107-110.
8. Smith S, Piacquadro D, Morhenn V et al. Short incubation PDT versus 5-FU in treating actinic keratoses. *J Drugs Dermatol* 2003;2(6):629-635.
9. Kalka K, Merk H, Mukhtar H. Photodynamic therapy in dermatology. *J Am Acad Dermatol* 2000; 42(3):389-413, quiz 414-6.
10. Itkin A, Gilchrist BA. Delta-Aminolevulinic acid and blue light photodynamic therapy for treatment of multiple basal cell carcinomas in two patients with nevoid basal cell carcinoma syndrome. *Dermatol Surg* 2004;30(7):1054-61.
11. Soler AM, Warloe T, Berner A et al. A follow-up study of recurrence and cosmesis in completely responding superficial and nodular basal cell carcinomas treated with methyl 5-aminolaevulinate-based photodynamic therapy alone and with prior curettage. *Br J Dermatol* 2001;145(3):467-471.
12. Touma D, Yaar M, Whitehead S et al. A trial of short incubation, broad-area photodynamic therapy for facial actinic keratoses and diffuse photodamage. *Arch Dermatol* 2004;140(1):33-40.
13. Issa MCA, Maceira J, Manela-Azulay M. Estudo da Remodelação Dérmica Induzida pela Terapia Fotodinâmica (MAL-TFD) na Pele Fotodanificada [Tese]. Rio de Janeiro: Universidade Federal do Rio de Janeiro, 2008.
14. Alster TS, Tanzi EL, Welsh EC. Photorejuvenation of facial skin with topical 20% 5-aminolevulinic acid and intense pulsed light treatment: a split-face comparison study. *J Drugs Dermatol* 2005;4(1):35-38.