

Original Articles

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The use of photodynamic therapy with methyl aminolevulinate and daylight for the treatment of actinic keratoses

O uso da terapia fotodinâmica com aminolevulinato de metila e luz do dia para tratamento de queratoses actínicas

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ABSTRACT

Introduction: Actinic keratosis (AK) is a pre-malignant lesion that can progress to squamous cell carcinoma. The diagnosis is through clinical, dermatoscopic and confocal microscopy assessment. Currently, the approach is the treatment of the field cancerization, comprising of clinically visible and subclinical AKs, for which photodynamic therapy (PDT) is a therapeutic option.

Objective: To evaluate improvement of AKs and cancerization field in patients submitted to daylight PDT, with clinical, dermatoscopic and confocal microscopy assessment.

Methods: Ten patients with multiple AKs on the face were selected. Daylight PDT was performed using methyl aminolevulinate and clinical, dermatoscopic and confocal microscopy photographic documentation was performed before and 60 days after the treatment.

Results: Of the nine patients who completed the treatment, 8 (88.8%) showed clinical improvement and reduction in the severity of AK with one treatment. On dermatoscopy, 4 patients (44.4%) showed significant improvement, 3 patients (33.3%) showed partial improvement and 2 patients (22.2%) had no change. On confocal microscopy, 6 (66.6%) patients presented reduction in the severity of the lesion.

Conclusions: Daylight PDT proved to be effective for the treatment of AKs, with high tolerability and efficacy, besides a good safety profile.

Keywords: Dermoscopy; Keratosis, Actinic; Microscopy, Confocal; Photochemotherapy

RESUMO

Introdução: A queratose actínica (QA) é lesão pré-maligna que pode progredir para carcinoma espinocelular. O diagnóstico é clínico, dermatoscópico e por microscopia confocal. Atualmente, aborda-se o tratamento do campo cancerizável, abrangendo QAs clinicamente visíveis e subclínicas, sendo a terapia fotodinâmica (PDT) uma opção terapêutica.

Objetivo: Avaliar melhora das QAs e campo cancerizável em pacientes submetidos a PDT com luz do dia, com análise clínica, dermatoscópica e por microscopia confocal.

Métodos: Foram selecionados dez pacientes, com múltiplas QAs na face. Realizada a PDT utilizando luz do dia com aminolevulinato de metila e feita documentação fotográfica clínica, dermatoscópica e por microscopia confocal antes do tratamento e 60 dias após seu início.

Resultados: Dos nove pacientes que completaram o tratamento, oito (88,8%) apresentaram melhora clínica e regressão no grau da QA com uma sessão. Na dermatoscopia, quatro pacientes (44,4%) apresentaram melhora significativa, três pacientes (33,3%) apresentaram melhora parcial e dois pacientes (22,2%) tiveram suas lesões estáveis. Na microscopia confocal, seis (66,6%) pacientes tiveram regressão no grau da lesão.

Conclusões: A PDT com luz do dia se mostrou eficaz para tratamento de QAs, apresentando alto grau de tolerabilidade e eficácia, além de bom perfil de segurança.

Palavras-chave: Ceratose Actínica; Dermoscopia; Fotoquimioterapia; Microscopia Confocal

INTRODUCTION

Actinic keratosis (AK) is one of the cutaneous lesions that most commonly progresses to squamous cell carcinoma (SCC), being a result of excessive exposure to ultraviolet light.¹⁻³ These lesions can undergo spontaneous regression, clinical stability or progression to SCC in a percentage ranging from 0.1 to 20% of cases in up to ten years.⁴ Its diagnosis is clinical, based on the presence of papules or erythematous plaques with white scales on photoexposed areas (face, scalp, chest and upper limbs).⁵ On dermoscopy, white scales and yellow follicular openings on an erythematous base can be seen, giving the aspect of pseudo-network or 'strawberry'.⁶ On confocal microscopy in vivo, an instrument of extensive applicability in the dermatological practice, that allows for the visualization on a cellular level with an almost histological resolution of cell and tissue features with a safe, noninvasive and real-time method,^{7,8} actinic keratoses can be seen by the hyperkeratosis (presence of white shiny scales on examination), irregular or atypical honeycomb pattern on the horny and granular layers of the epidermis and the presence of atypical keratinocytes.⁶

Treatment of actinic keratoses is important because it involves the prevention of progression of a pre-malignant lesion to squamous cell carcinoma, and many modalities can be used: cryotherapy with liquid nitrogen, surgical excision, curettage, topical medications (5-fluorouracil, trichloroacetic acid, imiquimod, ingenol mebutate and photodynamic therapy).^{2,4}

Lately, the treatment of the cancerization field has been approached, defined as the presence of multiple actinic keratoses on photoexposed areas, associated to the presence of dysplastic keratinocytes on the adjacent skin (interlesional). Thus, treatment of these areas involves both clinically visible actinic keratosis and subclinical lesions.⁵

Photodynamic therapy (PDT) is a treatment where selective destruction of the target tissue takes place through a photochemical reaction using a photosensitizing substance, light and oxygen.⁹⁻¹¹ This therapeutic modality can be used in the conventional form or with day light. In conventional PDT, the agents applied on the skin are later activated by specific light sources (broad spectrum lights, diode and laser lights) and are mainly employed for the treatment of actinic keratosis, low-risk basal cell carcinomas and Bowen's disease, with fast recovery and great cosmetic result.^{9,10} Daylight PDT is used for the treatment of grade I and II actinic keratoses, besides cancerization field. The substance applied is methyl aminolevulinate, that undergoes continuous metabolism into photoactive protoporphyrins, particularly protoporphyrin IX (PpIX), leading to an increased sensitivity to light only on the damaged cells.¹⁰ This way, with exposure to light, the molecules of activated porphyrins react with oxygen forming highly toxic reactive oxygen species (ROS), culminating in cell death.^{10,11}

The objective of this study was to evaluate the improvement on actinic keratoses and cancerization field in patients submitted to daylight photodynamic therapy with methyl aminolevulinate through clinical, dermoscopic and confocal microscopy analysis.

METHODS

From April 2016 to February 2017, 10 patients from the Outpatient Clinic of Dermatology from the Faculdade de Medicina do ABC, Santo André (SP), Fitzpatrick phototypes between I and III, older than 40 years, with multiple actinic keratoses (mostly grade I and II) on the face were selected; these patients signed the consent form and the study took place according to the ethical principles emanated from the Declaration of Helsinki. One lesion of actinic keratosis was selected on the face of each patient with clinical (Nikon DX AF-S Nikkor 18-105mm), dermoscopic (Dermoscope 3Gen DermLite®, United States) and confocal microscopy (VivaScope 3000 Caliber ID®, United States) photographic record before treatment and after 60 days.

Treatment consisted in cleansing the skin to be treated with aqueous chlorhexidine, superficial curettage of the scales of actinic keratoses, application of sunscreen without physical filters (Actinica® FPS 50, Galderma) and subsequent application of a thin layer of 16% methyl aminolevulinate (Metvix®, Galderma - France) all over the face (as guided by the product information), followed by continuous sun exposure for two hours, followed by removal of the product with plain washing of the skin, and instruction to spend the rest of the day indoors, without sun exposure.

Sixty days after performing daylight PDT, the patients were re-evaluated and new photographic documentation was performed. One patient was excluded from the study because she did not attend the re-evaluation after 60 days as previously agreed upon.

Response to treatment was graded from 1 to 4 (1: significant improvement; 2: partial improvement; 3: stable lesion; 4: worsening of the lesion) on three parameters evaluated: clinical aspect, dermoscopy and confocal microscopy.

RESULTS

Of the nine patients that completed the proposed treatment, four (44.4%) showed significant clinical improvement and four (44.4%) showed partial improvement. Therefore, eight of the nine patients (88.8%) improved the clinical aspect with regression of the grade of the actinic keratosis with one daylight PDT session.

Regarding dermoscopy, four patients (44.4%) showed significant improvement, being considered the improvement of the hyperkeratosis (scales) and the 'strawberry' pattern, and three patients (33.3%) showed partial improvement; this way, seven out of the nine patients (77.7%) showed improvement on the dermoscopic features. The two patients (22.2%) with stable lesion were graded like this, because even though they had initial improvement of the hyperkeratosis, there was early recurrence, determining a stable lesion.

Regarding confocal microscopy, four patients (44.4%) showed significant improvement, two patients (22.2%) showed partial improvement, so 66.6% of patients had regression on the grade of the lesion, evaluated by the improvement on the atypical honeycomb pattern, the hyperkeratosis and cell atypia.

These results, as well as the characteristics of the patients and the area of the lesions, are represented on table 1 and in figure 1. It is important to highlight that, besides the improvement on actinic keratoses evaluated clinically and dermoscopically, and by Confocal microscopy, all nine patients showed improvement on the global quality of the facial skin, both in lightening of hyperpigmentation and in smoothening of fine wrinkles and skin laxity, corroborating the findings of other studies that indicate photodynamic therapy as having an effect in the improvement of cutaneous ageing (Figure 2).

During the procedure, all patients classified the treatment as painless, attributing zero (ranging from zero to ten) to pain

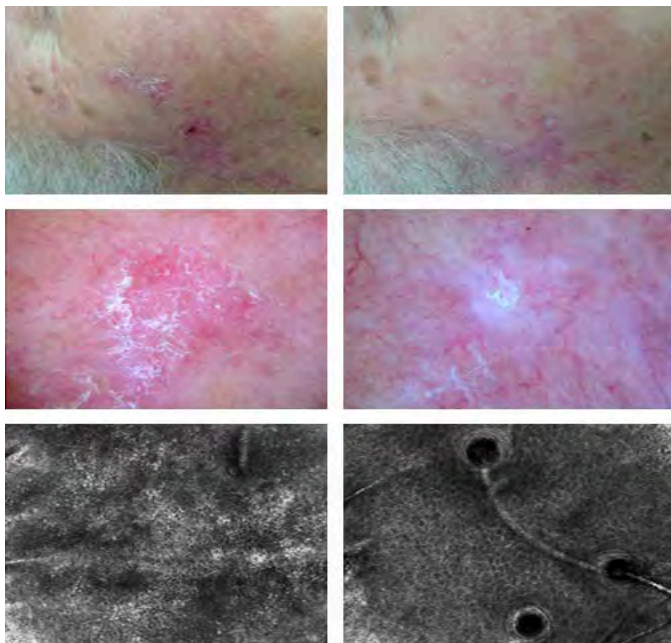


FIGURE 1: Actinic keratosis of patient 7: before (left) and after (right) treatment with one session of daylight photodynamic therapy; images demonstrate significant improvement in clinical aspect, dermoscopy (reduction of scales and erythema) and on confocal microscopy (improvement of the honeycomb pattern, which became more regular and typical)

during sun exposure. The patients developed erythema after treatment, that ranged from 1 to 4 days, and 2 patients had edema for 2 days.

DISCUSSION

Actinic keratoses represent the initial stage in the development of a squamous cell carcinoma and represent important markers for patients at risk of developing skin cancer.⁶ Multiple treatments are proposed aiming at regression and non-progression of these lesions to SCC, besides improvement in the cancerization field such as cryotherapy with liquid nitrogen, 5-Fluorouracil, Imiquimod and Ingenol Mebutate.^{4,5} Photody-

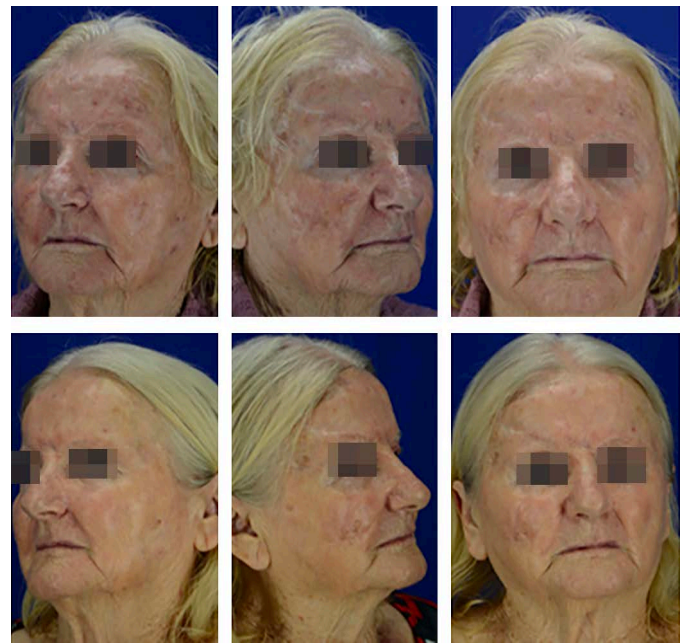


FIGURE 2: Improvement on the overall quality of the skin and laxity of the skin: before (top photos) and after (bottom photos) treatment with one session of daylight photodynamic therapy

TABLE 1: Profile of the participants and response shown after one session of daylight photodynamic therapy

Patient	Sex/Age	Area of the lesion	Clinical response	Dermoscopy response	Response on confocal microscopy
1	M/72	L Malar	1	1	1
2	W/44	R Malar	2	2	2
3	W/	L Eyebrow	2	2	3
4	W/	L Mandibular	1	1	1
5	M/67	L Malar	2	3	3
6	W/81	R Malar	3	3	3
7	W/80	R Pre-auricular	1	1	1
8	W/	R Malar	1	1	1
9	W/74	R Malar	2	2	2

L: LEFT; R: RIGHT

1: SIGNIFICANT IMPROVEMENT; 2: PARTIAL IMPROVEMENT; 3: STABLE; 4: WORSE

dynamic therapy, both conventional and daylight, has been widely used for the treatment of actinic keratoses and cancerization field, demonstrating similar efficacy between both modalities confirmed by randomized, multicentric studies like those by Wiegell,^{13,15,16,18} Rubel³ and Lacour *et al.*¹⁷ This study corroborates the efficacy of daylight photodynamic therapy for the treatment of AKs, since there was improvement of the lesions, with regression on their grade in most patients.

We also highlight the importance of the evaluation of these lesions with the aid of complementary diagnostic tools, such as dermoscopy and confocal microscopy. There are few studies using these methods to compare pre- and post-treatment lesions. Jafari *et al* studied 40 AKs with daylight PDT by clinical response and confocal microscopy and concluded that 80% of the lesions (n = 32) showed complete regression, 17.5% (n = 7) showed partial response and only one lesion remained unchanged; with confocal microscopy, they concluded that 57.5% (n = 23) of the lesions did not show cellular atypia and 40% (n = 16) showed little atypia, when compared to the pre-treatment assessment; they also observed improvement of the honeycomb pattern hyperkeratosis, which became more regular and typical.

Most patients of this study showed clinical (88.8%), dermoscopic (77.7%) and confocal microscopy (66.6%) improvement; however, we cannot state that there was total regression

of the lesions, a result that is not in keeping with the previous studies mentioned.

We also highlight that all patients were satisfied with the treatment, considered it painless and showed improvement on the overall quality of the facial skin, with smoother fine wrinkles, telangiectasias and erythema, results already previously seen when treating AKs and cancerization field with daylight PDT.¹⁹

This study has limitations such as small sample of patients (n = 9), lack of a control group and subjectivity in the exact qualification of diagnostic improvement, for example, for determining the grade of cellular atypia with confocal microscopy; however, the efficacy of the proposed treatment is certain.

CONCLUSION

Daylight photodynamic therapy proved to be effective for the treatment of actinic keratoses on the face, with improvement seen clinically, dermoscopically and on confocal microscopy. It is a treatment that represents an excellent option for the treatment of these lesions since it is well-tolerated by patients, highly effective, and has a good safety profile. ●

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