

Photodynamic therapy with delta-aminolevulinic acid and light-emitting diodes in actinic keratosis *

Terapêutica fotodinâmica com ácido delta-aminolevulínico e luz de diodos em ceratoses actínicas

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Abstract: BACKGROUND: Photodynamic therapy is a form of treatment in which a photosensitizing substance is applied to tissue and activated by a light source at a specific wavelength, thus selectively destroying cells. New light sources are being evaluated for use in the treatment of actinic keratoses.

OBJECTIVES: To evaluate the efficacy of photodynamic therapy with delta-aminolevulinic acid using a light emitting diode device as a light source in the treatment of actinic keratoses of the face and upper limbs.

METHODS: Eighteen patients with actinic keratoses of the face or upper limbs received an application of a 20% delta-aminolevulinic acid cream and were submitted to diode light irradiation at a wavelength of 630 nm.

RESULTS: A total of 328 actinic keratoses were treated, obtaining complete cure in 210 (64.0%) after 24 weeks. Lesions situated on the back of the hands were clinically cured in 49.2% of cases compared to 81.4% in the cases of lesions in other areas. There was no record of any severe adverse effects and patient satisfaction with the results was high.

CONCLUSION: Photodynamic therapy with a diode light emitting source proved effective and well-tolerated for the treatment of actinic keratoses, with results similar to those reported in the literature with other light sources.

Keywords: Keratosis; Photobiology; Photochemotherapy

Resumo: FUNDAMENTOS: A terapêutica fotodinâmica é técnica de tratamento em que se aplica uma substância fotossensibilizante nos tecidos ativada por uma fonte de luz de comprimento de onda específico, gerando destruição celular seletiva. Estudam-se novas fontes de luz que possam ser usadas no tratamento de ceratoses actínicas.

OBJETIVOS: Avaliar a efetividade da terapêutica fotodinâmica com ácido delta-aminolevulínico utilizando como fonte de luz um aparelho emissor de luz de diodos no tratamento de ceratoses actínicas de face e membros superiores.

MÉTODOS: Dezoito pacientes com ceratoses actínicas na face ou membros superiores realizaram uma aplicação de creme de ácido delta-aminolevulínico a 20% e foram submetidos à exposição de luz de diodos, comprimento de onda de 630 nm.

RESULTADOS: Foram tratadas 328 ceratoses actínicas, obtendo-se cura clínica completa em 210 (64,0%) após 24 semanas. Lesões do dorso das mãos apresentaram cura clínica completa em 49,2%; nas demais áreas esse valor foi de 81,4%. Não houve registro de efeitos adversos graves, e obteve-se bom grau de satisfação dos pacientes com os resultados.

CONCLUSÃO: A terapêutica fotodinâmica com fonte de emissão de luz de diodos mostrou-se eficaz e bem tolerada para tratamento de ceratoses actínicas, com resultados semelhantes aos encontrados na literatura utilizando outras fontes luminosas.

Palavras-chave: Ceratose; Fotobiologia; Fotoquimioterapia

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INTRODUCTION

Photodynamic therapy (PDT) is a form of treatment that is indicated for various dermatological diseases, particularly nonmelanoma skin neoplasias cancers and preneoplastic premalignant keratinocytic lesions. Its applications have been expanding in dermatology, and this technique and its efficacy have been tested in many studies in recent decades.¹⁻⁴

PDT is a non-invasive therapeutic method that uses the interaction between visible light and a sensitizing agent to generate cell death. The most widely tested sensitizing agents are delta-aminolevulinic acid (%ALA) and methyl aminolevulinic acid (MAL). %ALA is an amino acid that accumulates with a greater intensity in dysplastic cells and in those with rapid proliferation, and stimulates the production of protoporphyrin IX (PpIX) through enzymatic pathways on the heme biosynthetic pathway. When skin treated with %ALA is exposed to a light source that includes the absorption spectrum of PpIX (400-730 nm), it is photoactivated, generating reactive oxygen species and consequently resulting in causing cell death.⁵

Various light sources have been used in clinical studies with PDT, including lasers, xenon lamps, incandescent filament lamps and light emitting diode (LED) lamps; however, few studies have been conducted to compare these sources. Theoretically, photoactivation is obtainable with any visible light source, but its efficacy will vary depending on the wavelength generated, the total radiated power, the size of the field that is illuminated, the ease and cost of use and the flexibility to adapt its use to other photosensitizing agents. When applying the majority of light sources, it is attempted to use peak PpIX absorption of 630 nm (red) with the objective of maximizing tissue penetration.^{3,6}

LEDs are non-coherent light sources that generate a narrow spectrum of light (mean wavelength of 630 nm), which is ideal to activate the photosensitizer without generating the side effects found with more extreme wavelengths. They offer a continuous dose at optimal intensity, and for this reason, interest in their use in PDT has increased since they are considered to be safer and easier to use.⁷

The need to adapt previously established parameters to new light sources has motivated many publications.⁸⁻¹⁰ The objective of this series of cases was to evaluate the efficacy of PDT with %ALA, using a Brazilian-made LED device for the treatment of actinic keratoses (AK) of the face and upper limbs.

MATERIAL AND METHODS

Patients with a clinical diagnosis of AK on the face or upper limbs, who attended the Dermatology Department of the Porto Alegre Teaching Hospital,

Federal University of Rio Grande do Sul (UFRGS), University Teaching Hospital in Porto Alegre, Brazil, between July and August 2006, were selected for the study.

The inclusion criteria consisted of: at least 4 lesions on the areas to be treated; patient over 18 years of age, not pregnant, no history of photosensitivity, not in use of photosensitizing or immunosuppressive drugs and not having undergone any specific treatment for AKs in the previous 30 days.

Actinic keratoses were defined as small, scaly, well-defined single keratotic plaques located in areas subjected to chronic sun exposure.¹¹

Patients fulfilling these criteria were invited to participate in the study. They were duly informed with respect to the characteristics of the study and if they agreed to participate, they were asked to sign an informed consent form.

The study was initiated following approval of the ethical and methodological aspects of the protocol by the Internal Review Board of the Porto Alegre University Teaching Hospital, Porto Alegre, Brazil, of the ethical and methodological aspects of the protocol.

At the first visit, the patient's medical history was recorded and a complete dermatological examination was performed. The number of AKs per area was counted and the areas to be treated were photographed. If there was any doubt with respect to diagnosis, the lesions were biopsied. If histology indicated another diagnosis, the patient was excluded from the study.

The lesions to be treated were cleaned with 0.9% sterile saline solution and if scales or crusts were present they were removed by superficial curettage or microdermabrasion to facilitate penetration of the active substance. A non-ionic cream containing 20% ALA (Sigma Chemical Co., St. Louis, MO, USA) was applied to each lesion in a layer of approximately 0.1 cm, extending 0.2 to 0.5 cm onto the skin around the lesion. The lesions were occluded with plastic adhesive and aluminum foil, and after a three-hour incubation period were exposed to diode light radiation (Multi Waves[®], *Indústria Mecânica Fina*, São Paulo, Brazil), using a device that emits light at a wavelength of 630 nm, with an outlet output intensity of 3100 mW/cm², optical intensity 100 mW/cm² and an active surface area of 40/80 mm. The device was maintained at a distance of around 8 cm from the area to be treated. The periods of radiation varied from 25 to 30 minutes, with radiation of 100 mW/cm², generating total energy doses of 150-180 J/cm². These parameters were selected based on the manufacturer's recommendation for PDT with %ALA for in the treatment of AKs.

If the patient experienced any stinging burning sensation or pain during radiation, chilled saline solution was applied or vaporization was performed from a distance using liquid nitrogen to cool the area. The patients were instructed to use sunscreen with sun protection factor 30 and to avoid sun exposure on the treated area for 48 hours.

The topography of the lesions was divided into segments: forehead, right and left sides of the face, the bridge of the nosenasal dorsum, the back of the right and left hands, and the right and left forearms. If treatment was applied to more than one segment, each segment was treated at a separate session.

The study end-point outcomes were evaluated by the same examiner (CGR). Efficacy evaluation consisted of counting the AKs present in the area to be treated at three different moments (at the pretreatment consultation and at 12 and 24 weeks following application). Clinical cure of the AK was defined as the visual and tactile disappearance of the lesion in the treated area. The total cure rate and the rates corresponding to the different cure areas of the body were evaluated.

The patients were asked about the occurrence of erythema (absent, mild, moderate or severe), pain or a stinging burning sensation (absent, mild, moderate or severe), pruritus (absent, mild, moderate or severe), vesiculation (absent or present) and changes in skin pigmentation (absent or present) during consultations 2 and 24 weeks following application of PDT.

Finally, the patients were asked at weeks 2 and 24 whether they had felt discomfort during the treatment (no discomfort, mild discomfort, moderate discomfort or considerable discomfort that precluded repeating this treatment in the future) and were questioned regarding their satisfaction with the results of the treatment (very satisfied, satisfied, not very satisfied, unsatisfied).

The results referring to the study variables (total clinical cure, the presence of side effects, tolerance and patient's satisfaction with the method) were analyzed and presented descriptively as percentages.

RESULTS

A total of 328 AK lesions were treated in 18 patients in 29 different segments of the body, a mean of 18 lesions per patient. The majority of patients were male with an age of 64.6 ± 14 years (mean \pm standard deviation) (range 38-83 years). The back of the hands was the most commonly treated segment of the body, followed by the two sides of the face and the bridge of the nosenasal dorsum (Table 1).

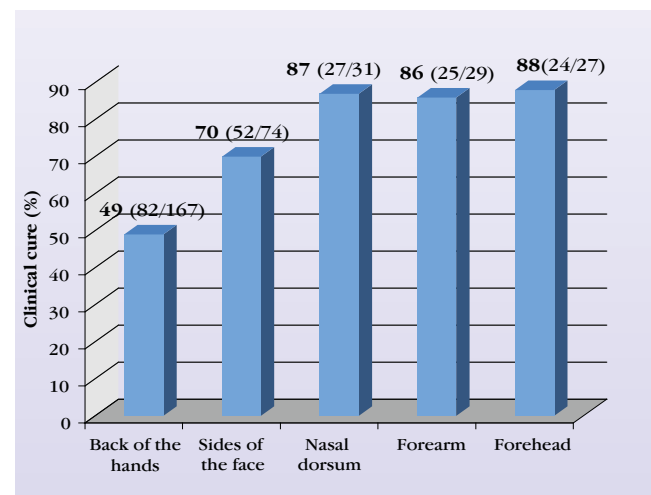
No patients were lost to follow-up and all were available for reevaluation at the consultations held 12 and 24 weeks after the procedure.

TABLE 1: Characteristics of the population of cases studied, demographic data and data on the lesions

Mean age of the study population	64.6 years
Study population	n (%)
Gender	
Male	11 (61.1%)
Female	7 (38.8%)
Location of the lesions treated	
Back of hands	167 (50.9%)
Sides of the face	74 (22.5%)
Nasal dorsum	31 (9.4%)
Forearm	29 (8.8%)
Forehead	27 (8.2%)
Number of lesions	328 (100%)

Of the 328 lesions treated, clinical cure was found reached in 214 (65.2%) at week 12 and in 210 (64.0%) at week 24. With respect to the evaluation according to body segment, 82/167 cases (49.2%) of actinic keratoses on the back of the hands were found to be clinically cured at weeks 12 and 24, whereas in the case of the lesions situated on the other segments of the body clinical cure was found in 131/161 cases (81.4%) at 12 weeks and in 128/161 cases (79.5%) at 24 weeks. Furthermore, when these segments were evaluated individually at week 24, clinical cure rates of 88%, 70%, 87% and 86% were found for the lesions treated on the forehead, the two sides of the face, on the bridge of the nosenasal dorsum and on the arms, respectively (Graph 1 and Figures 1-4).

All patients reported a stinging burning sensation and mild pain during radiation. Nevertheless, the great majority of patients tolerated the treatment well



GRAPH 1: Percentage of clinical cure of AKs according to the segment of the body treated, after 24 weeks

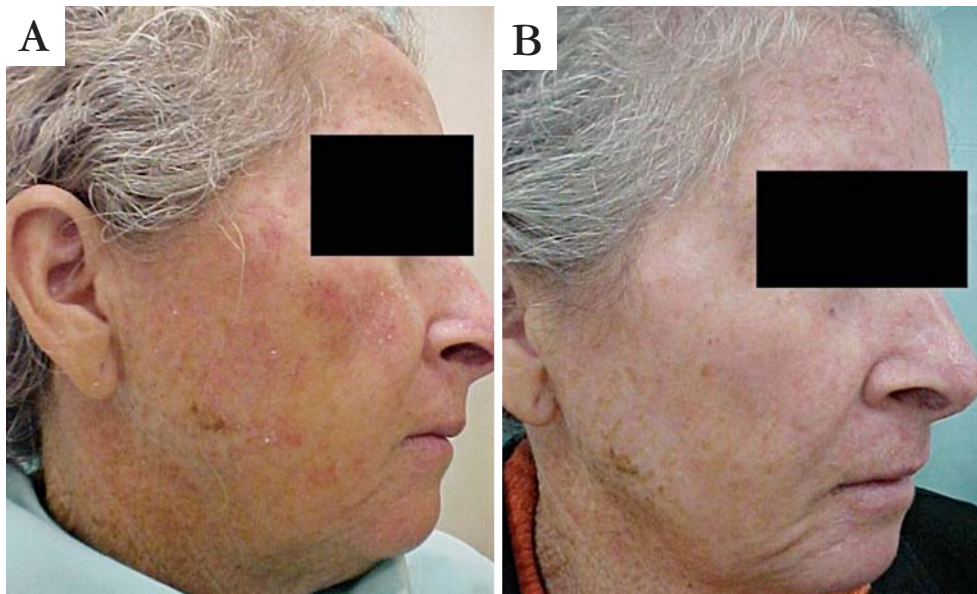


FIGURE 1: Actinic keratoses on the right side of the face prior to application of PDT (A) and at week 24 (B)

and continued therapy with no interruption. Nevertheless, in two patients, treatment had to be paused for a few minutes prior to completing radiation. The application was also interrupted in one patient at the sixth minute because of a painful stingingsevere burning sensation.

With respect to the side effects reported two weeks after treatment, 16 patients (88.8%) had experienced mild to moderate erythema, while 8 (44.4%) had mild pruritus and 5 (27.7%) reported pain or a mild stinging burning sensation. At 24 weeks, these symptoms were present in 11.1%, 5.5% and 0% of the patients, respectively. There was no record of vesiculation or dyschromias associated with the procedure at any of the visits.

The patients' opinion with respect to the treatment at week 2 showed that half reported experienced slight discomfort with the therapy, while at 24 weeks 12 patients (66%) reported no discomfort whatsoever (Table 2).

Regarding the results of treatment, half the patients reported that they were satisfied and only 1 (5%) was unsatisfied after two weeks. At week 24, patients' expression of satisfaction was even higher, with the great majority claiming to be satisfied or very satisfied with the results (Table 3).

TABLE 2: Opinion of the patients on the procedure (PDT) at weeks 2 and 24

	Week 2	Week 24
No discomfort	38% (7/18)	66% (12/18)
Mild discomfort	50 % (9/18)	27% (5/18)
Moderate discomfort	11% (2/18)	5% (1/18)
Considerable discomfort	0%	0%

DISCUSSION

Actinic keratosis (AK) is a preneoplastic lesion of keratinocytic origin associated with chronic sun exposure. It is an extremely prevalent skin disorder whose diagnosis is made by clinical examination in the majority of cases.¹¹

Various forms of treatment have been developed for AKs such as cryotherapy with liquid nitrogen, curettage, topical chemotherapy (5-fluorouracil), imiquimod and chemical peelings. These therapeutic options involve different degrees of efficacy and may be followed by different side effects such as secondary infection, slow healing, pain or discomfort, scarring and changes in pigmentation.¹²⁻¹⁵

In 1978, Dougherty et al.¹⁶ were the first to use PDT clinically. From that time onwards, it has been used to treat different types of tumor. In dermatology and, more specifically, for the treatment of AKs, open studies using PDT with δ ALA and non-coherent light in patients with AKs of the face and scalp reported cure rates of 71-100% following a single application.^{7,12,17-19} In a study conducted by this group using PDT with δ ALA and a non-coherent experimental light source, clinical cure was achieved in 65.7% of AKs treated with a single application.¹⁰

In addition, multicenter randomized studies

TABLE 3: Opinion of the patients regarding their satisfaction with the results of PDT at weeks 2 and 24

	Week 2	Week 24
Very satisfied	38% (7/18)	33% (6/18)
Satisfied	44 % (8/18)	61% (11/18)
Not very satisfied	11% (2/18)	5% (1/18)
Unsatisfied	5% (1/18)	0%

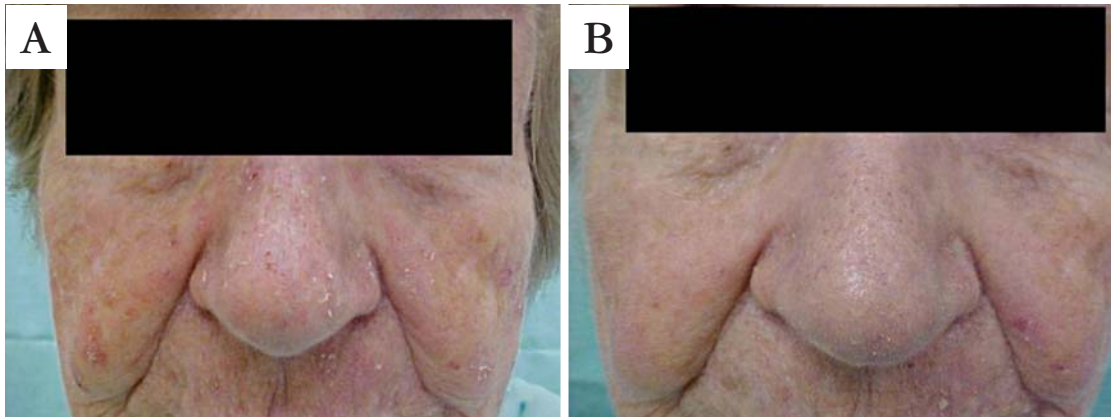


FIGURE 2: Actinic keratoses on the nasal dorsum prior to application of PDT (A) and at week 24 (B)

comparing PDT with longer established therapies for the treatment of AKs showed a similar efficacy between the groups; however, the esthetic outcome was significantly better in the group of patients who received PDT.^{13-15, 18-21} PDT has therefore been classified as a treatment option with good therapeutic selectivity, significant cure rates, good tolerability and favorable cosmetic results. Furthermore, it allows larger areas of the body to be treated, thereby enabling multiple actinic keratoses and areas affected by cancer to be treated simultaneously. The category of recommendation of this therapy is considered Level A and the evidence of its effectiveness for the treatment of non-keratotic actinic keratoses of the face and scalp is considered Level 1.¹⁵

Different lasers and non-coherent light sources have been tested for PDT. Since the coherence of light is lost after penetrating the skin to a depth of less than 1 mm, this property is not mandatory for the light source used in PDT. Radiation with non-coherent light sources is more practical, simpler and cheaper, and in general has been shown to be as effective as lasers.

LEDs correspond to a narrow band, non-coherent light source recently added to the range of possibilities for radiation in PDT. Studies have shown their efficacy *in vitro* and *in vivo* for the treatment of actinic keratoses, achieving rates similar to those found with other light sources.^{7,9}

One of these studies conducted by Juzeniene et al.⁸ compared two non-coherent light sources in PDT with MAL: one wide spectrum source (560-740 nm) obtained with a halogen lamp and another narrow band source (580-670 nm) obtained with a LED lamp. With respect to efficacy, *in vivo* findings showed that, compared to the halogen lamp, the LED lamp exerted a greater more profound effect on tissues, generated less heat and resulted in less pain when used in volunteers with healthy skin, while in animal models and cell culture it showed an efficacy similar to or better than that found with photoactivation of PpIX.

Using this same model of comparative evaluation of two non-coherent light sources, Babilas et al.⁹ successfully extended existing clinical findings data by treating patients with AKs. The results confirmed



FIGURE 3: Actinic keratoses on the forehead prior to application of PDT (A) and after 24 weeks (B)

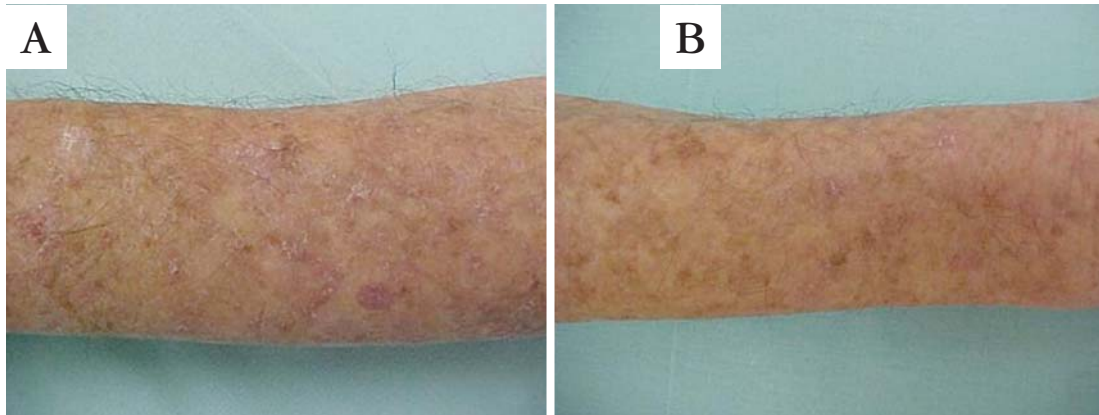


FIGURE 4: Back of the arm prior to application of PDT (A) and at 24 weeks (B)

what was already expected in terms of efficacy, with the use of LED for the treatment of AKs achieving very similar results to those found with the halogen lamp. We were extremely interested in this study, since it used methodology that was very similar to that used in the present study, with ALA as a photosensitizer and a practically identical technique of application. It differed, however, in that lower parameters were used for radiation (light intensity of 80 mW/cm^2 , total dose of radiated light 40 J/cm^2). Preliminary results were excellent; however, these were not sustained after 3 and 6 months.

Recently, Pariser et al.⁷ conducted a double-blind, randomized, placebo-controlled study of PDT with MAL for AK using a LED source; however, the parameters were also lower than those used in the present study. Cure rates obtained after three months were similar to those described in the literature with other lamps. Therefore, although few studies have been carried out, the results appear to confirm the efficacy of LEDs in PDT; however, comparison between studies is difficult, since the parameters used in the lamps were not uniform and other variables such as the use of ALA or MAL and the thickness and localization of the AK also affect results.

In the present study, complete cure was found in 64% of the lesions treated, a rate similar to those described in other reports from studies with similar designs, showing that the technique may be considered an effective alternative for the treatment of actinic keratoses. When the cure rate was evaluated in accordance with the segment of the body treated, clinical cure was found in only 49.2% of lesions on the back of the hands. Lesions on the forehead, on the two sides of the face, on the bridge of the nosenasal

dorsum and on the arms achieved clinical cure in 88%, 70%, 87% and 86% of cases, respectively. Similar findings have already been described in previous studies and may be due to the fact that the lesions on the extremities are in general thicker and more keratotic, consequently leading to poorer penetration of the photosensitizing agent, which may subsequently result in a poorer response to therapy.^{12,17,18,22,23}

In the present report, most of the patients tolerated the method well and satisfaction rates were favorable to the use of the technique. This shows that the use of PDT with ALA and diode lights is an alternative that is well-tolerated by patients. Studies involving a larger number of cases, principally those comparing the use of LED lamps with other modalities of PDT, may help define the different forms of PDT and the indication of the technique for the treatment of AKs.

CONCLUSION

PDT with δ ALA and diode emitting light sources was found to constitute an effective technique for the treatment of AK in this sample of patients, with clinical cure rates similar to those already published with the use of other light sources and other, widely established therapeutic techniques.

Efficacy of the treatment was greater in lesions on the face and arms, where the therapeutic response was excellent, better than that observed in the lesions situated on the back of the hands, in which the cure rate was lower.

After 24 weeks, no recurrences were found. The patients registered a favorable degree of satisfaction, both with respect to the preventive characteristics of the treatment and with the esthetic results and the low rate of significant side effects. □

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