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ORIGINAL ARTICLE

Daylight photodynamic therapy with methyl aminolevulinate cream is as effective as conventional photodynamic therapy with blue light in the treatment of actinic keratosis: a controlled randomized intra-individual study

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Abstract

Background We know the efficacy of daylight phototherapy dynamic (DL-PDT) in the treatment of actinic keratosis (AK). But the almost studies have compared daylight with red light using methyl aminolevulinate cream and not with blue light. PDT with blue light is another conventional PDT that is effective in the treatment of AKs.

Objectives The aim of this study is to assess the efficacy and the safety of DL-PDT vs. PDT in blue light in the treatment of AKs.

Methods This randomized, controlled, intra-individual efficacy and safety study enrolled 26 subjects. AKs on the face/scalp were treated once, with DL-PDT on one side and c-PDT on the contralateral side. Primary endpoints for DL-PDT at week 12 were efficacy with clearance of AKs and safety with assessment of pain. Lesions with complete response 12 weeks after one treatment session were followed until week 24.

Results More than 1000 AK were studied. At week 12, the raw number of disappeared AK lesions at 3-month follow-up was 19.6 (±6.0) for DL-PDT and 20.0 (±6.9) for c-PDT with $P = 0.8460$ (90.5% vs. 94.2% of AK disappearance, respectively). The response was maintained at 6 months (90.0% and 94.6% of AK reduction, respectively). DL-PDT was nearly painless than c-PDT with light blue: 1.2 vs. 5.1, respectively ($P < 0.0001$).

Conclusions Daylight-PDT seems as effective as c-PDT with light blue and DL-PDT is less painful. The response of DL-PDT was sustainable until 6 months.

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Conflict of interest

None.

Funding source

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Introduction

Daylight photodynamic therapy (DL-PDT) is emerging as a treatment of actinic keratosis (AK). Daylight is part of the daily therapeutic arsenal for extensive AK (grades 1 and 2). Several controlled studies have demonstrated the non-inferiority of DL vs. conventional PDT with red light using methyl aminolevulinate (MAL).[1–4] In view of these results, DL-PDT has been proposed as first-line treatment for multiple extensive AK since 2015 in accordance with EU recommendations.[5]

However, no study to date has compared DL-PDT with conventional PDT using blue light (c-PDT), which is another type of conventional PDT. Blue light is mainly used in North America. Blue light (400–410 nm) is interesting because it corresponds to the best absorption peak of protoporphyrin IX (PpIX). The principle behind PDT is that PpIX is absorbed after applying MAL to induce reactive oxygen species.[6] There is another absorption peak in red light (530–580 nm), but it is weaker. From a physical point of view, the absorption spectrum of PpIX should be better with blue light than with red light or daylight.[7]

The aim of this study is to evaluate the efficacy of DL-PDT compared to c-PDT with blue light on face and scalp AK lesions at 12 weeks and in terms of immediate pain.

Materials and methods

Study design

This was a randomized, controlled study on efficacy and safety where, for better comparability, patients also acted as controls. This monocentric study took place in central France (Limoges) between March 2015 and December 2016. The study was approved by the Agence nationale de sécurité du médicament et des produits de santé and the local ethics committee in France: Comité de protection des personnes du Sud-Ouest et Outre-Mer 4.

Patients

Patients included in the study were aged over 18 years and suffered from mild AK (defined as slightly palpable AK, better felt than seen) and possibly moderate AK (moderately thick, easily felt and seen). The patients also acted as controls for the purpose of treatment comparison. The study used a split-face and split-scalp design. Patients were required to have at least two comparable target areas on the face or scalp. Patients with at least two comparable fields of AK on the face and scalp, with a minimum of five AKs in each area, were eligible. The main exclusion criteria were pigmented lesions, hypertrophic AK, non-melanoma skin cancer, AK treatment in the last month, use of topical corticoids in the last 2 weeks, photosensitizing treatments or photosensitivity disorders and hypersensitivity to any MAL component.

Treatment

In order to accurately count lesion localizations and perform follow-ups, a clear plastic sheet was placed over each side of the face or scalp being treated and anatomical landmarks were marked on this sheet. Patients were randomized with regard to which side was exposed to daylight and which to blue light. Scales and crusts were gently removed, and the entire treatment area was superficially scraped. 16% MAL cream (Metvixia*; Galderma International, La Défense, France) was applied in a 1-mm thick layer to the entire treatment area and was kept uncovered on the side exposed to daylight and covered for 3 h on the side exposed to blue light. For the daylight area, patients exposed themselves continuously to daylight for 2 h, starting within 30 min of applying the MAL cream (Table 1). Exposure to daylight was allowed if the weather was not rainy and if the temperature was above 10°C.

For the blue light area, patients started blue light exposure 3 h after the MAL cream was applied, using a Waldmann PDT (Herbert Waldmann GmbH & Co, Villingen-Schwenningen, Germany) 450 lamp at 10 J/cm^2. The median duration of illumination ranged from 15 to 18 min.

Efficacy assessment

The primary endpoint was the raw number of AK lesions cleared at the 3-month follow-up for each side of the face or scalp after treatment.

The secondary endpoints were the raw number of AK lesions cleared at the 1- and 6-month follow-ups, calculated for each side of the scalp, and the raw number of new AK lesions at 1, 3 and 6 months after treatment. This was calculated for each side of the scalp.

For each of the above endpoints and for each patient, the difference between the DL-PDT and the c-PDT with blue light was calculated.

Moreover, the correlation between the daylight dose received and the response rate was made.

Safety assessment

The endpoints were the adverse events (AEs) reported during the study and the pain felt after each procedure, evaluated using a numerical scale from 0 (no pain) to 10 (extreme pain), just after exposure to the light.

Assessment of light dose

The effective daylight dose was measured using an electronic luxmeter (*LX100, KIMO® instruments*) placed next to the patient. The luxmeter takes real-time measurements during exposure. The unit used is lux.

Sample size

Following Wiegell,[1] we put forward the hypothesis that the smallest clinically significant mean difference would be 15%, with a standard deviation (SD) among patient responses of 25%. Based on an alpha risk of 5% and a power of 80%, at least 22

Table 1 Treatment procedures

Steps	DL-PDT	c-PDT (blue light)
Preparation	Remove scales and crusts with a curette Separate the 2 treatment areas with marker Application of MAL with 1-mm thick layer in AK surrounding 5 mm in normal skin	
Exposure	Daylight exposure starts 30 min after MAL application for 2 h in the garden of the hospital	Remove occlusive dressing after 3 h of MAL application Blue light illumination (10 J/cm^2 within 10 min)

c-PDT, conventional phototherapy dynamic; DL-PDT, daylight phototherapy dynamic; MAL, methyl aminolevulinate.

patients were required. We assumed that 20% of patients could be non-valuables for the primary endpoint; 26 patients were therefore included in the study.

Randomization

The randomization list was created by the Centre d'Epidémiologie, de Biostastiques et de Méthodologie de la Recherche (CEBIMER) of Limoges University Hospital using NQuery Advisor V7.0 (Statistical Solutions, Saugus, MA, USA) software and was balanced (ratio 1 : 1) with a mixed block size.

Randomization was ensured through sealed envelopes provided by CEBIMER, with the randomization order number and the trial names written on them. These envelopes were stored in a locked cabinet in the Dermatology Department.

Patients were randomized by the investigator during the inclusion visit.

Data analyses

Statistical analyses were conducted by CEBIMER using SAS V9.3 (SAS Institute, Cary, NC, USA) software. The significance level was set at $P < 0.05$ for all analyses and the statistics were produced according to the revised CONSORT 2010 Statements.[8]

Descriptive analyses

A patient flow chart was presented (Fig. 1) and the qualitative variables were described as instances of success and frequencies, while the quantitative variables were described according to their mean and SD.

Statistical analyses

Given that patients acted as their own controls and the endpoints did not follow a normal distribution (Shapiro–Wilk test), signed-rank tests for paired data were used to compare the differences in the number of AKs that had disappeared, the percentage of AKs that had disappeared, the number of new AKs and the pain evaluated with VAS, for both DL-PDT and c-PDT.

Results

Patients

Twenty-six patients were included in the study: 25 men (96.2%) and one woman (3.8%). The mean age was 75 years (range: 47.0–88.0). All patients were followed up for 6 months. No patient was lost during the follow-up period (Fig. 1). Light doses were measured in 23 patients.

The main characteristics of patients are presented in Table 2. The mean number of AKs on the daylight side is 21.7 per patient and 21.4 per patient on the blue light side. The total number of AKs treated was 1119.

Efficacy

As shown in Table 3, the mean number of cleared AK lesions at the 3-month follow-up was 19.6 (±6.0) for DL-PDT and 20.0

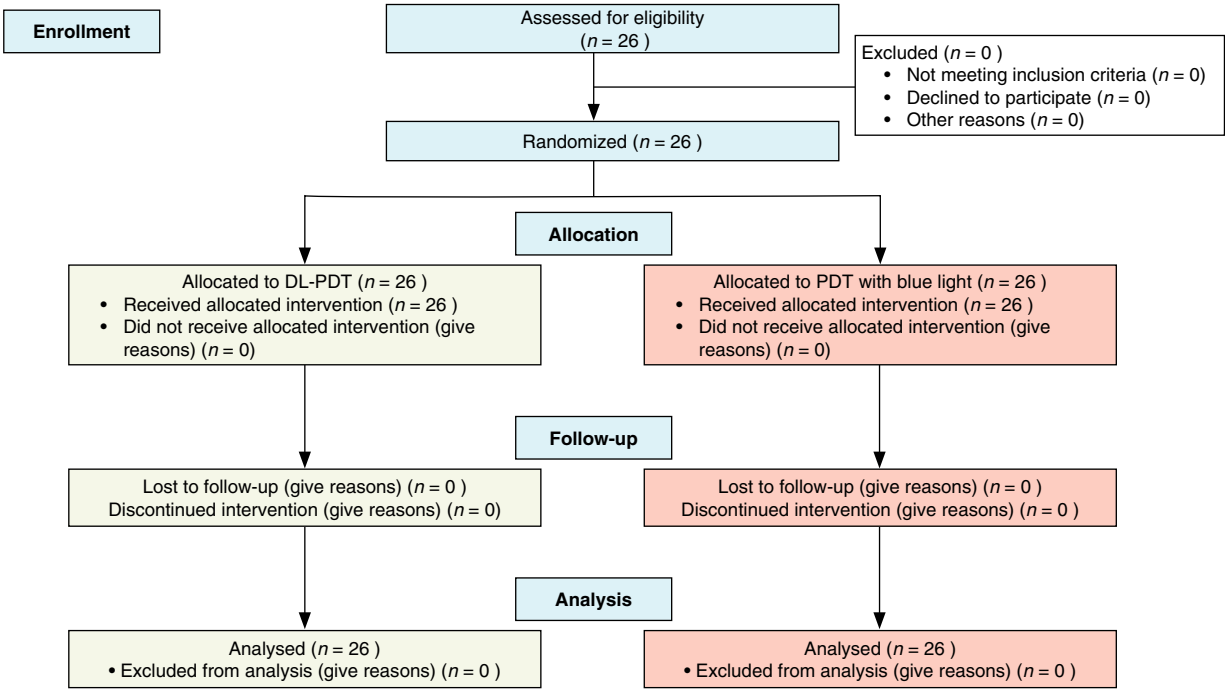

Figure 1 Subject disposition (flow chart).

Table 2 Baseline demographics and disease characteristics (Intention to treat)

	Total *N* = 26	
Sex (%)		
Male	25 (96)	
Female	1 (4)	
Age (years)		
Mean ± SD	74.5 ± 0.9	
Min–Max	47–88	
Race (%)		
White	26 (100)	
	MAL DL-PDT	**MAL c-PDT**
Number of lesions per subjects		
Mean ± SD	21.7 ± 6.5	21.4 ± 7.7
Min–Max	13.0; 39.0	11.0; 37.0
Total number of AKs treated	563	556

AK, actinic keratosis; c-PDT, conventional phototherapy dynamic; DL-PDT, daylight phototherapy dynamic; MAL, methyl aminolevulinate.

Table 3 Mean patient AK lesion counts in blue light-treated areas and daylight-treated areas at baseline and 3-month follow-up

Ak lesion count	c-PDT Mean (±SD)	DL-PDT Mean (±SD)	*P*-value
Baseline	21.4 (±7.7)	21.7 (±6.5)	
Raw number of cleared AK at 3 months (%)	20 (±6.9) 90.5%	19.6 (±6.0) 94.2%	0.846†

†Signed-rank test for paired data.
No significant differences were found between blue light and daylight-treated areas.
AK, actinic keratosis; c-PDT, conventional phototherapy dynamic; DL-PDT, daylight phototherapy dynamic; MAL, methyl aminolevulinate.

(±6.9) for c-PDT with $P = 0.8460$ (90.5% vs. 94.2% lesions cleared, respectively).

For the secondary endpoints, the results are shown in Fig. 2. There was no significant difference between the two treatments after 1 month and after 6 months ($P = 0.8528$ and $P = 0.8828$, respectively). At the 6-month follow-up, the mean number of cleared AK lesions was 19.7 (±6.2) for DL-PDT and 20.2 (±7.3) for c-PDT (90.0% and 94.6% lesions maintained cleared, respectively).

As regards the recurrence of lesions, there were more new lesions after DL-PDT than after c-PDT, with a difference between these two treatments of 0.6 ± 0.8 ($P = 0.0007$) after 3 months and a difference of 1.3 ± 0.9 ($P < 0.0001$) after 6 months of treatment (Fig. 3). No significant difference was found at 1 month ($P = 0.3750$).

Efficacy and light dose

The mean daylight dose was 59.9 Klux (±37.3). No statistically significant correlations were found between the daylight dose and the percentage of cleared AKs at 1 month [Rho = 0.33, 95% CI (0–0.10; 0.64), $P = 0.1217$], 3 months [Rho = 0.10, 95% CI (−0.32; 0.48), $P = 0.6446$] and 6 months [Rho = 0.04, 95% CI (−0.37; 0.43), $P = 0.8618$], which indicates that the efficacy of DL-PDT is not affected by weather conditions.

Safety

Daylight-PDT was significantly less painful than c-PDT (Fig. 4). The mean pain score for DL-PDT was 1.2 (±1.9) and 5.1 (±2.3) for c-PDT ($P < 0.0001$). No patient stopped blue light exposure prematurely due to pain.

No treatment-related AEs were observed.

Discussion

Several randomized studies have proven the non-inferiority of DL-PDT vs. PDT with red light.[2,3,9–13] This is the first randomized study comparing daylight exposure with blue light exposure in PDT for the treatment of AKs. No statistical difference in terms of efficacy was found between DL-PDT and c-PDT, with a mean difference of cleared AKs of 0.5 ± 6.2 ($P = 0.8460$) between the two sides. The proportional reduction in AKs at 3 months was more than 90% for both treatments. These results were expected because most of the spectrum of daylight is within the blue wavelength range.

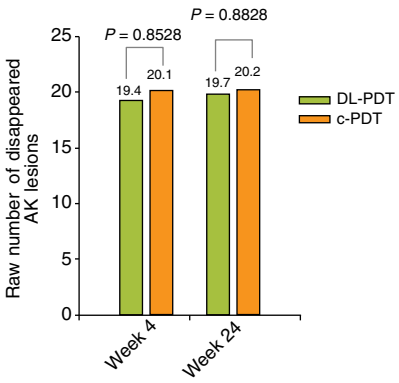

Figure 2 Secondary efficacy endpoint at week 4 and week 24.

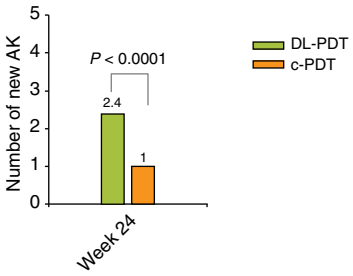

Figure 3 Number of new actinic keratosis after treatment.

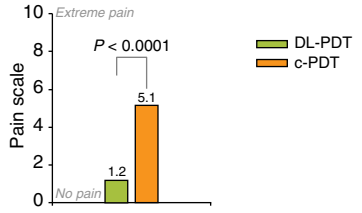

Figure 4 Evaluation of pain: superiority of daylight phototherapy dynamic (DL-PDT) (Intention to treat).

These results are interesting because of the high number of AKs (1119).

A few studies (comparing daylight to red light) involved follow-ups for up to 6 or even 12 months.[2,11–13] Our study showed that the response was maintained at 6 months, with a reduction of more than 90% when using DL-PDT. A systematic review was performed in 2019 and only three studies on AKs reported a 12-month long-term efficacy of MAL DL-PDT,[12,14,15] but only one study was compared to red light in AKs. In 2017, Fargnoli *et al.*, found that the 12-month clearance rate was significantly higher for c-PDT with red light than with DL-PDT through a study on 35 patients, treating a total of 672 AKs. In Fargnoli's study[12], the lesion response rate was 76% by conventional PDT and 66% of those treated by DL-PDT ($P < 0.01$). In our study, there were more patients with new lesions at 6 months when using DL-PDT, with a difference of 1.3 AKs (±0.9 ($P < 0.0001$). It is valuable to know that relapse can be greater with DL-PDT than PDT with blue light, even if the difference in the number of new AKs after treatment is small. Patients treated with daylight PDT must be closely monitored. In 2015, Fargnoli *et al.*[13] found a recurrence rate after 6 months of 17% and 12% with DL-PDT and c-PDT, respectively, with a statistical difference that was not further reported in the long-term results in 2017 after 12 months: 13% vs. 10%, respectively, with no statistical difference.[12]

On the other hand, this study confirms that DL-PDT is less painful than c-PDT, even with blue light (pain score: 5.1 ± 2.1 vs. 1.2 ± 1.9 for DL-PDT and c-PDT respectively, $P < 0.0001$). Continuous production and activation of PpIXfor 2 h with DL-PDT could explain the better pain tolerance.[1] With c-PDT with blue light, the 3 h of MAL incubation induces an accumulation of PpIX with an acute activation under red or blue light, which could explain the greater pain.[1] DL-PDT has also been shown to be better tolerated in terms of treatment-related AEs.

Daylight-PDT is convenient and easy to administer. Most patients were treated in autumn and winter, and there was no correlation between the light dose and DL-PDT's efficacy. There was no impact from the light dose – all patients showed a good response to daylight exposure. According to EU recommendations, DL-PDT must meet only two weather conditions: a temperature above 10°C and no rain.[5]

Moreover, DL-PDT is convenient because MAL application is shorter than for conventional PDT (30 min vs. 3 h) and does not require an occlusive dressing.

Another advantage of DL-PDT is that it does not require hospital care. It requires a consultation to apply the photosensitive cream (Metvixia*) for 30 min, after which patients expose themselves the daylight. The recommendation is to use a chemical sunscreen 15 min before skin preparation on all sun-exposed skin, with SPF >20 to block UV with no physical filters so as to let visible light through.[5,16]

The study's limitations should nevertheless be acknowledged. This study was not investigator-blinded. However, a high number of AKs were evaluated (more than 1000) and the study was intra-individual, with subjects acting as their own controls. Moreover, it is the first study to compare blue light and methyl aminolevulinate cream, and the analyses focused on the intention to treat. Furthermore, the length of follow-up (6 months) is relatively accurate for a chronic disease.

In conclusion, the study confirmed that DL-PDT is as effective and less painful than c-PDT with blue light for face and scalp AK, with no dose relation to light dose. It also confirms the high maintenance of AK lesion clearance at the 6-month follow-up in a population with multiple AKs. Compared to Fargnoli's results at 6 months, our findings suggest a higher risk of relapse for DL-PDT patients, which suggests that these patients should be closely monitored or even retreated earlier.

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