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Low-level light-assisted photodynamic therapy using a wearable cap-like device for the treatment of actinic keratosis of the scalp

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ABSTRACT

Background: Daylight photodynamic therapy (dlPDT) is a painless and increasingly cost-effective treatment for actinic keratosis (AK). New protocols avoid incubation, minimizing pain and adverse events. However, it is time-consuming and dependent on specific weather conditions. In patients with AK of the scalp, we evaluated the efficacy of indoor photodynamic therapy (PDT) using a wearable low-level light therapy (LLLT) device, without pre-incubation with a photosensitizing agent.

Methods: In this pilot study, 27 patients with thin and moderately thick AK (Olsen Grades I-II) underwent a single 15-minute session of LLLT using a wearable cap-like device immediately after application of methyl-aminolevulinate (MAL) cream, with no prior preparation of the affected area. Treatment efficacy was quantified by measuring the reduction in AK lesion number and the AK quality of life (AKQoL) score. All AK lesions were mapped at baseline for follow-up 2 months later. Paired pre/post scalp biopsies from 5 patients were analysed using histological and immunohistochemical techniques (p53, p27, cyclin D1, p63, and Ki67 expression). Data were analysed using the Wilcoxon signed-rank test.

Results: In all patients we observed a global reduction in the number of AK lesions (71%; $p < 0.0001$) and AKQoL score (from 5.6 to 4.4; $p = 0.034$) 2 months after treatment. Histology and immunohistochemistry of skin biopsies from 5 patients also revealed marked improvements after LLLT. No patients reported any pain during treatment.

Conclusion: PDT using LLLT is a rapid, painless, and efficacious modality for the treatment of AK.

1. Introduction

Photodynamic therapy (PDT) is a commonly used procedure for the treatment of non-melanoma skin cancer and precancerous conditions, including actinic keratosis (AK) [1–3]. In the case of AK, PDT also fulfils the need for field cancerization treatment, which is essential to prevent the development of new lesions [4,5]. Daylight PDT (dlPDT) is a recently described PDT modality in which solar radiation is used as the light source for the photosensitizer [6,7]. Daylight photodynamic reactions are initiated without prior incubation of a photosensitizer [8]. This modality has proven efficacious and versatile, and causes no pain (which is intrinsically related to incubation time and not the light source used). However, this technique suffers from several limitations, including a lack of control on the part of the physician, dependence on weather conditions (in some countries this technique cannot be used during the coldest months of the year), and over-exposure to

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deleterious radiation, including ultraviolet light [9].

Low-level light therapy (LLLT) using lasers and light-emitting diodes (LED) is emerging as an alternative form of PDT, for which a growing number of potential indications have been identified [10–12]. Although interpretation of the results of certain studies may suffer from bias and the proposed therapeutic efficacy of this technique is not reproduced in some settings, evidence supports the use of LLLT to treat certain dermatological conditions. These include neuropathic pain in herpes zoster patients [13], oral lichen planus [14], and hair disorders [15] such as androgenetic alopecia (AGA) (clinical evidence level Ib) [16]. Indeed, cap-like apparatuses housing light emitting diodes (LEDs) are currently used for the treatment of AGA [17]. Similar devices containing light emitting fabrics may serve as useful light sources for PDT, as they provide homogeneous field illumination and low but consistent light irradiance [18,19]. However, to date LLLT devices have not been thoroughly tested for use in PDT procedures. In this study, we evaluated the efficacy of PDT using red LED LLLT, administered using a wearable cap-like device.

2. Materials and methods

2.1. Patients

A prospective interventional pilot study was conducted at the Department of Dermatology of the Ramón y Cajal University Hospital (Madrid, Spain) between February and July, 2017. Patients with at least 5 A K lesions (grades I-II) were considered eligible for inclusion. The primary exclusion criterion was the presence of grade III AK lesions or skin cancer. Other exclusion criteria are listed in Fig. 1. The medical and dermatological history of all patients (including prior AK treatments) was recorded. None of the patients had undergone field cancerization treatment during the preceding 6 months. Patients were consecutively recruited until a size sample of 30 individuals or significant results were reached.

This study was approved by the Ethics Committee of the Ramón y Cajal University Hospital (038-17). All participating patients provided written informed consent.

2.2. Treatment

AK lesions on the scalp were photographed, numbered, classified and mapped using a transparent plastic film template consisting of 25 squares (9-cm^2 each) (Thermo-Cell Test®, Monaderm, Monaco). The lesions were classified according to the Olsen clinical classification as follows: grade I, mild (slightly palpable AK lesion, more easily palpated than seen); grade II, moderate (moderately thick, easily palpated AK lesion) [20,21]. Without performing any pretreatment procedure, a 1-mm layer of 16% methyl aminolevulinate (MAL) cream (Metvix®, Galderma, Switzerland) was applied to the entire treatment area and left uncovered. A cap-like domiciliary device (Skymedic, Terrassa, Spain) (see Fig. 2) housing 246 high-powered unfocused LEDs and capable of emitting red light at a maximum wavelength of 630 nm and a bandwidth of 20 nm (mean irradiance, 5.1 1 ± 0.48 mW/cm^2) was placed on the head of each patient for 15 min immediately after MAL cream application. The total dose of red light administered was 4.59 J/cm^2. Light emission was measured using a Macam SR-2271 double monochromator spectroradiometer (Irradian CO, Scotland, UK) connected to an Ulbrich integrating sphere. In all cases the procedure was performed by the principal investigator, and there were no significant procedural variations between patients. Upon completing LLLT, the photosensitizer was removed using gauze soaked in 0.9% saline solution. Sunscreen containing inorganic filters was applied to the treated area, and patients were advised to continue to apply sunscreen for the following days. To assess the level of pain experienced, all patients provided a score on a visual analogue scale (VAS, scored from 0 to 10) every 5 min during treatment and upon completion. Patients were also asked to report any treatment-related symptoms. After each treatment the internal surface of the device was cleaned using chlorhexidine alcohol solution.

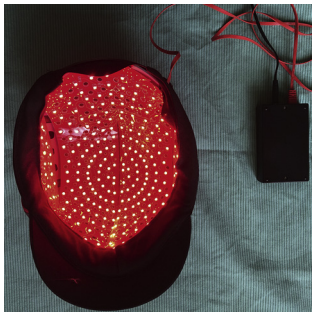

Fig. 2. Image showing the LED surface of the device. The 246 unfocused high-powered LEDs emit light at a wavelength of 630 nm.

2.3. Biopsy

In 5 randomly selected patients, scalp lesions were biopsied and the

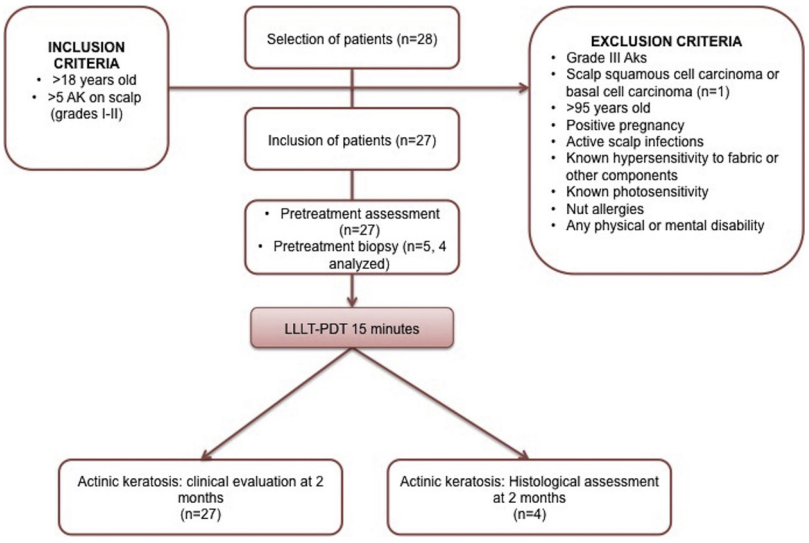

Fig. 1. Flow chart showing detailed inclusion and exclusion criteria.

lesion location mapped. Two months later, a second biopsy was taken from the mapped location, but not the exact same position (to avoid complete removal of the lesion). All lesions selected were at least twice the size of the biopsy punch used. The biopsied material was fixed in formalin, embedded in paraffin, and processed for routine histological examination (hematoxylin-eosin [H&E] staining). Immunostaining was also performed to detect p27, p53, cyclin D1, p63, and Ki67, as previously described [22,23]. Immunohistochemistry results were analysed qualitatively. Biopsies obtained at baseline and 2 months later were evaluated by the same pathologist (MLGM).

2.4. Efficacy assessment

The primary criterion for measuring efficacy was the reduction in the total number of AK lesions, regardless of subtype. The reduction in lesion number according to subtype was also quantified. AK lesions were identified by palpation (thickness and roughness) with bare hands and based on their clinical appearance (scaly, erythematous papules). Two months after LLLT, patients underwent a follow-up examination during which the pre-existing AK lesions were identified using the template created at baseline.

A second outcome measured was the reduction the in score attributed to each patient upon completion of the Actinic Keratosis Quality of Life (AKQoL) questionnaire [24] after treatment. The version of the questionnaire used had been adapted for Spanish patients and validated accordingly [25].

2.5. Data analysis

The primary outcome measure (decrease in the total number of AK lesions) was analysed per-protocol. The Wilcoxon signed-rank test was used to evaluate changes in AK lesion number and in AKQoL score 2 months after LLLT. Statistical analyses were conducted using SPSS 21.0 (IBM-Corp, Armonk, NY), with a p-value < 0.05 considered statistically significant.

3. Results

3.1. Patients

In total, 27 patients, all male (mean age, 77.37 years; range, 60–88 years), were included in the study. Sixteen patients were classified as Fitzpatrick's skin phototype III (59.3%) and 11 (40.7%) as phototype II. Sixteen patients (59.3%) had arterial hypertension and 6 had diabetes (22.2%). A total of 430 actinic keratosis lesions (grade I, n = 285; grade II, n = 145) were identified as suitable candidates for therapy. Most patients had previously undergone treatment using the following therapeutic modalities: cryotherapy, 66%; conventional PDT (cPDT), 55.6%; topical agents (e.g., imiquimod, ingenol mebutate, 5-fluorouracil), 18.5%. Only 5 patients (18%) had not undergone any previous treatment.

3.2. Therapeutic efficacy

Therapeutic variables and the total number of AK lesions at baseline and after 2 months of follow-up are shown in Table 1. Overall, we recorded a 71% decrease ($p < 0.0001$) in the number of AK lesions 2 months after treatment. Stratifying by lesion subtype, the numbers of subtype I and subtype II lesions were reduced by 71% ($p < 0.0001$) and 71.8% ($p < 0.001$), respectively (Fig. 3). Two months after treatment, the mean AKQoL score was 4.384/27, as compared with 5.59/27 at baseline ($p = 0.034$). No significant difference in mean VAS score was observed between baseline and 2 months of follow up ($p = 0.368$). The following treatment-related symptoms were reported: mild heat, 7 patients (25.9%); mild paraesthesia, 2 patients (7.4%). Eighteen patients (66.7%) reported no treatment-related symptoms.

3.3. Histological data

Microscopic analysis of biopsied lesions revealed that 4 out of the 5 samples corresponded to AK lesions (1 hypertrophic, 1 Bowenoid), while one corresponded to seborrhoeic keratosis (this biopsy was excluded from the immunohistochemical study). Analysis of the 4 baseline AK biopsies revealed actinic damage with solar elastosis in the underlying papillary dermis. Analysis of biopsies obtained 2 months after PDT revealed overall normalization, as evidenced by thinning of the epidermis and a reduction in solar elastosis (Fig. 4). Immunostaining showed a decrease in the levels of expression of p53, cyclin D1, and Ki67 2 months after PDT as compared with baseline (Fig. 5). Other histological findings are shown in Table 2.

4. Discussion

In this study, we describe a 71% reduction in the number of AK lesions 2 months after treatment in patients who underwent red-LED LLLT using a wearable cap-like phototherapy device. No differences in treatment efficacy were observed across lesion subtypes. The high therapeutic efficacy observed might be due to the short distance between the target area and the LEDs housed in the phototherapy device; this prevents light dispersion and ensures more uniform irradiation of the treatment area than usually achieved with red LED lamps. Although this was not a comparative study, the observed rate of lesion clearance appears comparable to that reported in patients treated with dlPDT or topical agents [26], and superior to that obtained with other therapeutic modalities such as cryotherapy [27].

Analysis of the 4 biopsies obtained 2 months after treatment revealed a significant reduction in hyperkeratosis and cytological atypia, and an almost completely normal epidermis. Immunohistochemistry showed a marked reduction in the expression of the cell proliferation markers p53, Ki67 and cyclin D1, in agreement with previous findings in patients treated with cPDT [22,23]. Another interesting finding was the significant decrease in the AKQoL score 2 months after treatment. This may be due to the decrease in the number of AK lesions on the scalp. The fact that all patients were male may have contributed to the low AKQoL score recorded at baseline, as sex may influence AKQoL score [24,28–30]. For each 5-minute period analysed during treatment,

Table 1
Clinical outcomes with low-level light assisted photodynamic therapy.

CLINICAL VARIABLES (n = 27)	TOTAL AK		GRADE I AK		GRADE II AK		AKQoL		VAS (mean) (0-10) SD = 0.69		
	PRE	POST	PRE	POST	PRE	POST	PRE	POST	5'	10'	15
DATA VALUE	430	124	285	83	145	41	5.59	4.38	0.52	0.555	0.52
	Clearance: 71.2%		Clearance:71%		Clearance: 71.8%						
p VALUE	< 0.0001		< 0.0001		< 0.0001		0.034		0.368		

AK: actinic keratoses; AKQoL: actinic keratoses quality of life index; VAS: visual analogic scale; SD: standard deviation.

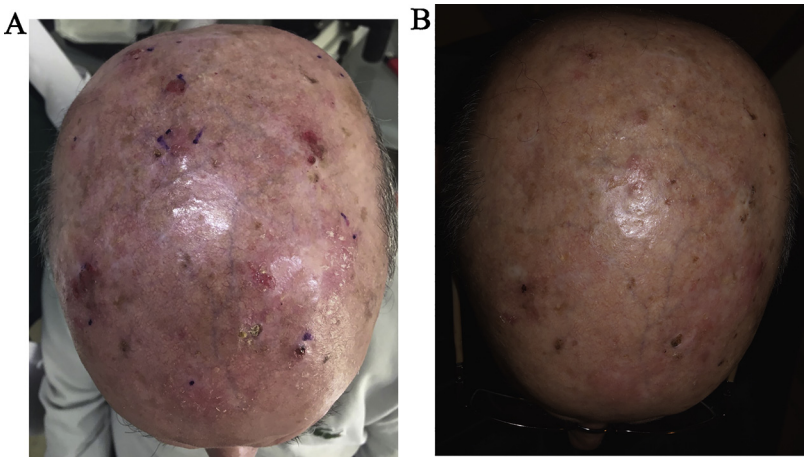

Fig. 3. A. Eroded grade I and II AK lesions on the scalp of an aged patient with intense photodamage. B. AK lesion number is markedly reduced after a single session of LLLT (MAL application followed immediately by red LED irradiation for 15 min at 630 nm and 4 J/cm^2).

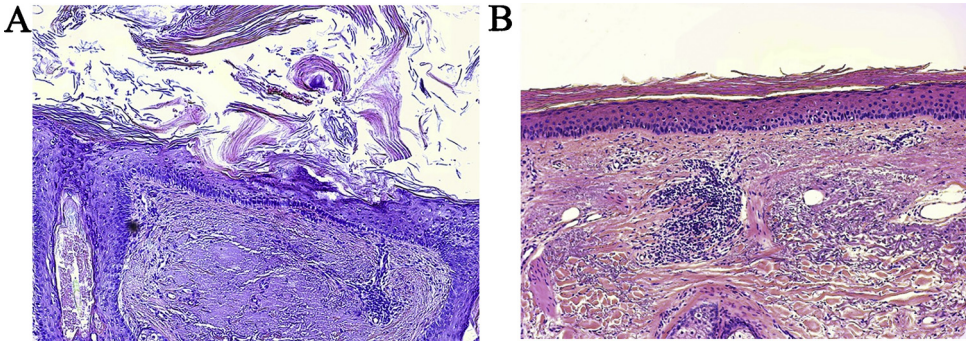

Fig. 4. A. Pre-treatment biopsy showing intense hyperparakeratosis with atypia compatible with a diagnosis of actinic keratosis (H&E ×100). B. Normalization of the epidermis with the attenuation of atypia and hyperkeratosis after LLLT (H&E ×100).

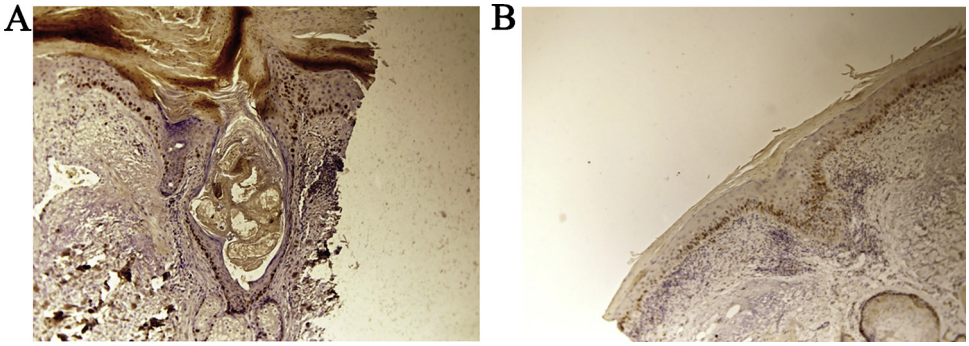

Fig. 5. A. Immunohistochemistry showing increased expression of p53 in the basal and intermediate epidermal layers. B. Immunohistochemistry 2 months after treatment showing a global reduction in p53 expression, which is confined to the basal layer.

the mean VAS score was < 1/10, with no differences observed over time, indicating a very low level of pain throughout the entire procedure. Indeed, none of the patients reported any discomfort during treatment, hypothetically due to the minimal, albeit sufficient, levels of protoporphyrin IX (PpIX) and the low level of irradiance of the device. Taken together, these results indicate that this type of treatment is well tolerated.

PDT is a well-established treatment for AK and is improving continuously. Although highly efficacious, it does cause varying degrees of pain and discomfort during treatment [3,31]. Recent studies have evaluated the use of several novel protocols and light sources in PDT [32,33] with a view to decreasing the lower light fluence used or shortening incubation times, and thereby reducing discomfort and increasing tolerability. In their 2006 study of PDT administered using a domiciliary device, Moseley and coworkers reported a high level of efficacy and excellent tolerance [34]. This was followed several years later by the development of "Ambulight", a home PDT device, with very good outcomes in the treatment of non-melanoma skin cancer [35]. Around the same time, Wiegell and coworkers demonstrated that daylight photodynamic therapy (dlPDT) is an efficient and efficacious option for the treatment of AK, and does not cause the pain associated with cPDT [36]. A minimum light fluence of 3.5 J/cm [2] was established for dlPDT [7], and a light intensity of more than 5000 lx found to be effective [9]. Evidence indicates that the use of a higher fluence has no effect on dlPDT efficacy, and may actually result in more adverse events [37]. A recent study has even pointed that there is no established minimum luminance threshold for dlPDT [38].

There is a growing interest in the use of low-level light sources,

Table 2
Histological outcomes in the four patients.

PATIENT Nº	H&E- DESCRIPTION		Thickness		Atypia		P27/KI		P53		CYCLIN D1		P63		KI67	
	PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST
1	Hypertrophic AK	Loss of hyperparakeratosis, thinned epidermis, normalization of basal layer	(+++)	(+)	(++)	+	(-)	(+)	(/)	(/)	(++)	(+)	(++) In higher layers of epidermis	(+)	(+++)	(+), restricted to basal layer
2	AK	Normalization and thinning of epidermis	(++)	0	(++)	(+)	(+)	(+)	(+++)	(-)	(++)	(+)	(++) In higher layers of epidermis	(++)	(++)	(+)
3	Bowenoid AK	Thinning and residual dysplasia in the basal layer	(+++)	(+)	(+++)	(+)	(++) Basal and spinous layer	(+)	(+++)	(++)	(-)	(+)	(+++)	(++)	(+++)	(++)
4	Actinic keratosis	Ordering and thinning of epidermis	(+++)	(-)	(+++)	(-)	(/)	(+)	(++)	(+)	(++)	(++)	(++)	(++)	(++)	(+)

PRE: pretreatment; POST: post treatment; AK: Actinic keratosis; (-): lack of presence or expression; (+): mild expression; (++): moderate expression; (+++): intense expression; (/): artifact or not valid data.

Fig. 6. Simultaneous treatment of 2 patients using wearable LLLT devices.

including diode lasers and LEDs, in medical applications, and several such devices for the treatment of hair disorders are already commercially available. The device used in the present study emits red light at a wavelength of 630 nm with a low bandwidth, and produces a sufficiently high radiation dose to exert a therapeutic effect within a short period of time. We hypothesize that the homogenous radiation of the entire scalp enabled by this device may account for the high degree of efficacy despite the low radiation dose used. Throughout the entire cancerization field, which is fully and homogeneously illuminated by the red LEDs in the device, photosensitivity reactions and PpIX accumulation occur promptly and sequentially in the active dysplastic cells of the AK lesions [39]. Importantly, this low-radiation protocol was not preceded by incubation of the photosensitizing agent, potentially avoiding adverse reactions and cell necrosis and apoptosis in unaffected tissue. Despite the omission of the incubation stage, the accumulation of body heat in the scalp beneath the wearable device, combined with the increase in skin temperature caused by a 15-minute exposure to red LEDs, may have promoted PpIX production, which is known to occur in response to increases in temperature [40]. As such, the true rate of PpIX production in our patients may have been underestimated. Although the light sensor connected to the spectroradiometer recorded low radiation levels, it also indicated a very intense homogeneous light field on the skin covered by the device. We hypothesize that the AK cells not only received direct radiation from the closest LED, but also reflected and dispersed light from nearby LEDs, thereby amplifying the light field.

Histologically verified therapeutic effects of PDT on cancerization fields within 6 weeks of treatment have been previously described [41]. Based on those reports, we designed this pilot study to assess the efficacy of red LED LLLT two months after treatment. Given the reported relationship between treatment-associated pain and the duration of incubation of photosensitizing agents [36], we eliminated the incubation step in order to minimize pain and improve tolerability. Several studies of *in vitro* PDT [42] and dlPDT have reported good therapeutic efficacy after incubation times ranging from 0 to 30 min [43].

During this study several patients were treated simultaneously within a small-enclosed space (Fig. 6), indicating that the LLLT procedure used is practical, as well as time efficient (15 min with concurrent treatments). Furthermore, the therapeutic device is relatively low cost, especially when compared with other commercially available LED lamps for PDT, which are approximately 10 times more expensive than wearable LLLT head devices. Furthermore, this modality is less painful than cPDT, and, in contrast to dlPDT, can be performed all year round, regardless of weather conditions, latitude and season. Patients can also be monitored throughout the procedure, ensuring clinical control.

Limitations of our pilot study include the relatively small sample size, the lack of a comparative interventional group (treated with dlPDT or cPDT) or control group, a lack of blinded assessment in order to avoid bias, and the short follow-up time (2 months).

In conclusion, our results show that MAL-PDT of the scalp using a wearable LLLT device is efficacious for AK of the scalp. Further studies should be designed and conducted to compare the efficacy of LLLT with that of cPDT or dlPDT.

Conflicts of interest

None.

Funding sources

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