

CLINICAL REPORT

Laser-mediated Photodynamic Therapy: An Alternative Treatment for Actinic Keratosis?

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Photodynamic therapy (PDT) with light emitting diode (LED) illumination is a frequently used treatment modality for actinic keratosis (AK) with excellent cosmetic outcome. A major disadvantage, however, is the high pain score. Pulsed dye laser (PDL) illumination has been suggested, but the long-term efficacy of this treatment is unknown. In this split-face study we prospectively treated 61 patients with AK, with both LED-PDT and PDL-PDT. The mean change in the number of lesions between the end of follow-up and start of therapy was -4.25 (95% confidence interval (95% CI) -5.07 ; -3.43) for LED-PDT and -3.88 (95% CI -4.76 ; -2.99) for PDL-PDT, with a non-significant difference ($p=0.258$) of -0.46 (95% CI -1.28 ; 0.35). The percentage decrease from baseline in the total number of AK was 55.8% and 47.8%, respectively, at 12-month follow-up. Visual analogue scale pain score was lower after PDL (mean 2.64) compared with LED illumination (mean 6.47). These findings indicate that PDL-PDT is an effective alternative illumination source for AK when pain is a limiting factor for regular LED-PDT. Key words: pulsed dye laser; actinic keratosis; photodynamic therapy.

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Actinic keratosis (AK) is the most prevalent precancerous skin condition, resulting from chronic exposure to ultraviolet (UV) radiation. It is predominantly located on chronically sun-exposed skin, such as the head, neck and the dorsal aspects of the hands (1). Prevalence is especially high among individuals with fair skin type or among individuals taking immunosuppressant medication (2). Typically, multiple AKs co-exist in a photo-damaged area and recurrence tends to be high, probably as a result of field cancerization (3, 4). This stresses the need for (repetitive) field-directed treatments.

Several interventions are currently used for the treatment of AK. Liquid nitrogen cryotherapy is the most

frequently used therapy worldwide (5). However, this is a lesion-directed treatment and has limited use in areas of field cancerization. In contrast, field-directed therapies have the potential to treat subclinical lesions, resulting in lower recurrence rates (6, 7). Among the most frequently used field therapies are topical 5-fluorouracil cream, imiquimod cream, ingenol mebutate gel, diclofenac gel and photodynamic therapy (PDT) (8).

The mechanism of PDT is based on the interaction between photosensitizing agents, such as 5-aminolevulinic acid (5-ALA) or methyl-aminolaevulinic acid (MAL), and a light source (9, 10). For this purpose, non-coherent light emitting diodes (LED) are used in daily practice (11).

A major disadvantage of non-coherent light sources is high pain experience, especially in patients with multiple AK. This is a major drawback for follow-up treatments (12).

Previous research aimed at optimizing PDT by attempting to reduce pain, offer shorter treatment duration and shorter down times. One example is illumination with a long-pulsed pulsed dye laser (LP-PDL) (13). Despite promising results regarding equal efficacy with fewer side-effects, it remains unclear whether this efficacy is maintained at long-term follow-up (13–15). Our study compared the treatment efficacy of LED-PDT with PDL-PDT, using a long-term follow-up.

METHODS (for complete details see Appendix S1¹)

Patients

Participants were recruited and treated at a secondary dermatology referral centre in the Netherlands. Inclusion criteria were: age 18 years or older, Fitzpatrick skin type I–III and a clinical diagnosis of AK on the scalp and/or forehead (minimum area 25 cm²). Exclusion criteria were: suspicion of malignancy in the treatment area, use of immunosuppressive medication, any topical treatment in the past 6 months within the treatment area, known hypersensitivity for the photosensitizer or presence of other skin conditions in the treatment area. The study was approved by the local medical ethics review board (16). All patients gave their written informed consent.

Procedures

The total number of target lesions in the treatment area of each individual participant was scored. Lesion severity was assessed

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sed using the Olsen scale (1 = mild (slightly palpable, more easily felt than seen); 2 = moderate (moderately thick, easy to see and feel); 3 = severe (very thick AK)). Two clinically equal treatment areas were assigned. Subsequently, both areas were pre-treated with slight curettage, followed by application of methyl-aminolevulinate cream (Metvix®, Galderma Benelux, Rotterdam, the Netherlands). Both areas were covered with an occlusive light-blocking tape. After 3 h, all participants received PDL illumination on the left side of the treatment area (595-nm pulsed dye laser, Vbeam, Candela Corporation®, Wayland, MA, USA; 7-mm spot size, fluence 7 J/cm², pulse duration 10 ms, epidermal cooling with Dynamic Cooling Device (DCD spray/delay) 30/10 ms, spots overlapping 50%) and regular LED illumination on the right side (Aktilite®, Galderma Benelux, Rotterdam, the Netherlands, 37 J/cm², 635 ± 18 nm).

Outcome assessment

Follow-up visits were scheduled at 3, 6, 9 and 12 months. During each follow-up the number of target AKs was calculated. Adverse events were recorded with questionnaires. Pain scores were assessed using a visual analogue scale (VAS 0–10).

Statistical analysis

The primary outcome measure was defined as the mean change in the number of lesions between baseline and 12-month follow-up. A *t*-test for paired samples was conducted to test the difference in mean decrease between treatments. The sample size of this study with 57 patients enabled detection of a between-treatment difference (in mean decrease in AK lesions with a standard deviation (SD) of 3) of 1.6 or more, with a power of 80%.

Other continuous outcomes were also tested for statistical significance, with a *t*-test for paired samples. Differences in proportions between treatments were tested using the McNemar test for paired proportions. All analyses were performed on an intention-to-treat basis. *p*-values smaller than or equal to 0.05 were considered as a significant difference.

RESULTS

A total of 61 male patients, with a mean age of 73.7 years (range 57–87 years) and Fitzpatrick skin type I–III, were included. Baseline characteristics are shown in Table I. A total of 1,041 AKs (531 PDL, 510 LED) with a mean Olsen score of 2.02 and 2.07 for LED and PDL illumination, respectively, were included. A total of 57 patients were treated and completed follow-up. The other 4 patients were lost to follow-up because travelling distance or severe health problems prevented them from attending follow-up visits. One patient was not able to complete LED illumination, due to extensive pain sensation. This patient was subsequently treated with PDL illumination on both treatment areas, but was analysed in the LED group. Two patients were illuminated with the same treatment regimen again at 3 months follow-up, due to no or little clinical response in both treatment areas.

Efficacy

The mean decrease in number of lesions from baseline to 12-month follow-up was –4.25 (95% CI –5.07; –3.43) for LED-PDL and –3.88 (95% CI –4.76; –2.99) for PDL-

Table I. Relevant baseline characteristics for both pulsed dye laser (PDL) and light emitting diode (LED, Aktilite) illumination

	PDL illumination (n=61)	LED illumination (n=61)
Age, years, mean ± SD	73.7 ± 7.5	73.7 ± 7.5
Sex, n (%)		
Male	61 (100)	61 (100)
Female	0 (0)	0 (0)
Fitzpatrick skin type, n (%)		
I	14 (22.9)	14 (22.9)
II	45 (73.8)	45 (73.8)
III	2 (3.3)	2 (3.3)
Number of AK lesions per patient		
1–5	14 (23)	17 (27.8)
6–10	32 (52.5)	28 (46)
11–15	11 (18)	13 (21.3)
>15	4 (6.5)	3 (4.9)
Total lesions included, n	531	510
Baseline total AK lesions, mean ± SD	8.70 ± 3.98	8.36 ± 3.79
Olsen grade (lesions), n		
1	6 (9.8)	9 (14.7)
2	45 (73.8)	42 (68.9)
3	10 (16.4)	10 (16.4)
Lesion location		
Scalp, n (%)	50 (82)	50 (82)
Forehead, n (%)	11 (18)	11 (18)

AK: actinic keratosis, SD: standard deviation.

PDL. The negative sign indicates a decrease in number of AK lesions in both groups. Hence, the difference between treatments in mean number of lesions was –0.46 (95% CI –1.28; 0.35) with a SD of 3.04 (*p* = 0.258).

The relative decrease in total number of lesions from baseline (as a percentage of the number of AK lesions at baseline) was 47.8% and 55.8% for PDL and LED illumination, respectively, at 12-month follow-up. Table II shows all the relevant outcome measurements. The percentage of patients with better, equal or worse efficacy of LED compared with PDL illumination were 48.2, 21.4 and 30.4, respectively.

The McNemar test showed no significant difference in global clinical improvement between both treatment groups (*p* = 0.625). A total of 89.3% of patients showed clinical improvement after PDL vs. 92.9% after LED illumination.

Side-effects

VAS pain score after PDL was significantly lower than after LED, with a mean VAS score of 2.64 (SD 1.84) and 6.47 (SD 2.17) for PDL and LED, respectively. The mean difference (PDL minus LED) was –4.55 (95% CI –4.06; –5.05, *p* < 0.01). Mean treatment duration for PDL was 1.45 min, compared with a predetermined 7.23 min for LED illumination.

Table III demonstrates the percentages of patients who reported side-effects. Burning sensation was reported significantly more often after LED illumination compared with PDL. Two patients developed a local skin infection

Table II. Relevant outcome measurements for both light emitting diode (LED) and pulsed dye laser (PDL) illumination during follow-up

	Baseline	3 months	6 months	9 months	12 months
LED					
Lesion decrease, mean (95% confidence interval)	–	–4.93 [–4.10;–5.76]	–5.17 [–5.97;–4.37]	–4.75 [–5.57;–3.93]	–4.25 [–5.07;–3.43]
Total number actinic keratosis	510	197	183	204	225
Cured number actinic keratosis	–	313	327	306	285
Decrease from baseline, %	–	61.4	64.1	60.0	55.8
PDL					
Lesion decrease, mean (95% confidence interval)	–	–5.11 [–5.80;–4.42]	–5.29 [–6.15;–4.43]	–4.61 [–5.44;–3.78]	–3.88 [–4.76;–2.99]
Total number actinic keratosis	531	223	203	236	277
Cured number actinic keratosis	–	308	328	295	254
Decrease from baseline, %	–	58.0	61.8	55.6	47.8

in the LED treatment area, which was subsequently treated with topical antibiotic ointment (Fucidin cream, 20 mg/g, Leo Pharmaceuticals, Amsterdam, The Netherlands). The skin healed without any residual changes in both patients.

Patient preferences

Of the patients treated with PDL illumination, 78.7% would definitely undergo this treatment again vs. 32.8% of the patients treated with LED illumination ($p < 0.01$). Furthermore, 4.9% of patients treated with PDL illumination would definitely not undergo another treatment vs. 19.7% of the patients treated with LED illumination ($p = 0.013$).

DISCUSSION

PDL illumination is a quick, patient-friendly and safe treatment for mild-to-moderate AK (13, 14). To our knowledge, the present study is the first to demonstrate efficacy data with long-term follow-up. Our results indicate that both illumination sources result in a similar decrease in AK lesions between baseline and 12-month follow-up.

The similar effectiveness of PDL and LED is consistent with other studies that reported results after shorter follow-up duration. Aleksiadis-Armenakas (13), studied the use of LP-PDL (595 nm) illumination after either 3 or 14 to 18 h incubation time with topical 5-ALA cream. They concluded that it is a safe and effective treatment, with minimal discomfort and rapid recovery times. Specifically, the mean percentage of lesions cleared after one treatment at 8 months follow-up was 90.3%. However, the number of patients who completed the 8-month follow-up was small and little information about statistical analyses is given (13, 17–19). Other studies with a 1–3 month follow-up period reported no difference in efficacy between LED and PDL. These results, however, cannot be compared with our study as they had a shorter follow-up period and were performed within a smaller population (14, 15).

The exact mechanism behind the PDT response is not fully understood. PDT is mediated by oxygen-dependent

photochemical reactions. In epithelial neoplasms the topical photosensitizer is metabolized into protoporphyrin IX (PpIX) following illumination with visible light (20). Excitation of photosensitizers, such as 5-ALA or MAL, results in the formation of cytotoxic free radicals and singlet oxygen. These target cellular and mitochondrial membranes, resulting in apoptosis and necrosis (14, 21, 22). It is hypothesized that by dividing light exposure into several shorter pulses, there might be time for tissue re-oxygenation. This principle can be seen in pulsed laser systems. PDL illumination does trigger apoptosis, but because there is time for re-oxygenation in between pulses, there might be less tissue ischaemia. A paper by Togsverd-Bo et al. (23) describes the amount of photobleaching (the depletion in photosensitizer fluorescence intensity) using different light sources. They conclude that LED produces significantly higher photobleaching compared with LP-PDL. The median photobleaching percentages of LED at a dose of 37 J/cm² were 91% and 98%, compared with 43% and 52% after LP-PDL at 7.5 J/cm². This might explain the lower pain experience during PDL illumination.

Pain is a major concern among physicians and a major disincentive to patients to undergo new PDT treatments in the future. Our results show that pain scores are high following LED-mediated PDT, while pain sensation during PDL illumination is significantly lower. Our results also indicate a higher patient preference for PDL over LED illumination.

In previous studies several factors that might influence pain sensation during PDT have been described (24, 25). The presence of a dynamic cooling device, fast operation speed and the ability to work with longer pulse durations with non-purpuric effects, may all contribute to lower pain sensation in patients after PDL illumination (17, 18).

Table III. Frequency of adverse events one week post-treatment

Adverse events	PDL, n (%)	LED, n (%)	<i>p</i> -value*
Burning sensation	13 (21.3)	43 (70.5)	<0.001
Erythema	54 (88.5)	59 (96.7)	0.095
Crusting	3 (4.9)	11 (18.0)	0.033
Infection	0 (0)	2 (3.3)	0.248

*McNemar test for paired proportions.

LED: light emitting diode; PDL: pulsed dye laser.

Air-cooling for example reduces the level of pain sensation during illumination (26, 27). However, the amount of PpIX photobleaching is reduced when, for example, air-cooling devices are used, which might influence efficacy (28). Wiegell et al. (29) suggested that pain sensation was directly related to the amount of PpIX formation prior to illumination. Another hypothesis is that photosensitizing agents are transported into peripheral nerve-endings, thereby triggering nerve stimulation (30, 31). The presence of apoptosis and necrosis, together with an inflammatory reaction, presumably contributes to the burning sensation as well. In addition to a lower pain sensation, other studies show that PDL illumination can also result in side-effects, such as erythema and burning sensation, albeit to a smaller extent (14, 17, 18). Our results support these observations.

Despite the possible benefit of pain reduction, shorter treatment duration and fewer adverse events, PDL illumination has various disadvantages that should be taken into account. Relatively high costs, the need for special supplies and expertise to use the device are the most important ones. Not every hospital has a PDL device. Both PDL and LED illumination are in-hospital treatments. Several studies have been done to assess efficacy of daylight as illumination source for the PDT response with the supposed advantage of less pain during the procedure (32–35). These studies show non-significant differences between the efficacy of daylight and LED illumination and report high patient satisfaction, less pain sensation and a better time- and cost-effectiveness. Daylight PDT is therefore also a good alternative in cases in which pain is a limiting factor. However, in Europe it cannot be performed throughout the year. PDL-PDT is therefore a good alternative in winter. The shorter total duration of PDL-PDT compared with daylight-PDT, is also an advantage.

A limitation of the present study is the open-label non-randomized study design and the fact that the patients and investigator were not blinded. Also, newly developed lesions post-treatment were not differentiated from persistent lesions in analysis. In addition to the presence of side-effects, the duration of side-effects was not assessed.

To conclude, AK is a chronic lifetime skin condition with frequent relapses. Our results show that PDL illumination can be performed rapidly, resulting in lower pain sensation, and is an acceptable alternative illumination source when pain is a limiting factor for regular LED illumination.

Conflict of interest: N.W.J. K-S participates in the advisory board of Galderma.

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