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Photodynamic therapy of multiple actinic keratoses: reduced pain through use of visible light plus water-filtered infrared A compared with light from light-emitting diodes

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Summary

Background Photodynamic therapy (PDT) with methyl aminolaevulinate (MAL) is an effective treatment for multiple actinic keratoses (AKs). Pain, however, is a major side-effect.

Objectives To compare pain intensity, efficacy, safety and cosmetic outcome of MAL PDT with two different light sources in an investigator-initiated, randomized, double-blind study.

Methods Eighty patients with multiple AKs grade I–II were assigned to two groups: group 1, MAL PDT with visible light and water-filtered infrared A (VIS + wIRA); group 2, MAL PDT with light from light-emitting diodes (LEDs), with a further division into two subgroups: A, no spray cooling; B, spray cooling on demand. MAL was applied 3 h before light treatment. Pain was assessed before, during and after PDT. Efficacy, side-effects, cosmetic outcome and patient satisfaction were documented after 2 weeks and 3, 6 and 12 months. Where necessary, treatment was repeated after 3 months.

Results Seventy-six of the 80 patients receiving MAL PDT completed the study. Patient assessment showed high efficacy, very good cosmetic outcome and high patient satisfaction. The efficacy of treatment was better in the group of patients without spray cooling ($P = 0{\cdot}00022$ at 3 months, $P = 0{\cdot}0068$ at 6 months) and showed no significant differences between VIS + wIRA and LED. VIS + wIRA was significantly less painful than LED: the median of maximum pain was lower in the VIS + wIRA group than in the LED group for PDT without spray cooling. Pain duration and severity assessed retrospectively were less with VIS + wIRA than with LED, irrespective of cooling.

Conclusions All treatments showed high efficacy with good cosmetic outcome and high patient satisfaction. Efficacy of treatment was better without spray cooling. VIS + wIRA PDT was less painful than LED PDT for PDT without spray cooling.

Actinic keratoses (AKs) are squamous cell carcinomas (SCCs) in situ. AKs can progress to invasive SCCs. Therefore, national and international guidelines recommend the treatment of AKs.[1] Photodynamic therapy (PDT) with 5-aminolaevulinic acid (5-ALA) or its ester methyl aminolaevulinate (MAL) is an established treatment option. PDT is an effective and safe procedure with an excellent cosmetic outcome.[2]

One of the major side-effects of PDT of multiple AKs is local pain during the application of light, as the skin surface is densely innervated by pain fibres. The degree of the painful sensation varies depending on the choice of the light source.[2] The Hydrosun® radiator type 505 (Hydrosun Medizintechnik GmbH, Müllheim, Germany) uses a halogen lamp and emits visible light (VIS) and water-filtered infrared A (wIRA), whereas a device with light-emitting diodes (LEDs) (Aktilite® CL 128; Galderma, Bruchsal, Germany) emits mainly VIS. The efficacy of the LED device (Aktilite® CL 128) in clearing AKs with 5-ALA and MAL (Metvix®; Galderma) PDT has already

been examined in several studies and is well documented.[3] The halogen radiator (Hydrosun® type 505) has not been investigated for PDT of AKs in a larger, double-blind study so far. The VIS + wIRA device is known to reduce pain in a variety of indications and to increase tissue oxygen partial pressure, temperature and metabolism,[4] which may improve the efficacy of PDT.

Therefore, one aim of the study was to compare the clinical efficacy, pain and side-effects using these two devices when applied according to the manufacturers' recommendations and to the typical clinical use of these devices in PDT of multiple AKs with different spectra and irradiation times.

Patients and methods

This investigator-initiated, randomized, double-blind study was previously approved by the local ethics committee of the RWTH Aachen University Hospital and the competent government authority (BfArM, Germany). Investigations were performed in accordance with the national and international Good Clinical Practice guidelines and the Declaration of Helsinki.

All patients had given informed consent prior to participation in the study. Eighty white patients with untreated, non-pigmented grade I–II AKs of the face or scalp were selected. The following criteria led to exclusion from the study: age under 45 years or over 85 years, immunosuppression for idiopathic, disease-specific or therapeutic reasons, porphyria or known hypersensitivity to porphyrins, known photodermatoses or photosensitivity, known allergy to MAL, pregnancy, lactation, diagnosis of basal cell carcinoma or hyperkeratotic AK, as well as intake of photosensitizing pharmaceuticals; topical treatments with corticosteroids, retinoids, 5-fluorouracil or imiquimod during the last 2 weeks; systemic treatments with retinoids, chemotherapy or immunotherapy during the last 3 months; laser resurfacing, chemical peels, cryotherapy or PDT during the last 2 months; participation in other studies within the last 3 months. Eighty patients received MAL PDT, 76 of whom completed the study (Table 1).

Table 1 Baseline characteristics of all patients

	VIS + wIRA PDT, n (%)	LED PDT, n (%)
Gender, number (%) of patients		
Male	35 (87·5)	36 (90)
Female	5 (12·5)	4 (10)
Age (years), median (range)	69 (56–84)	70 (57–85)
Fitzpatrick skin type		
I	3 (7·5)	4 (10)
II	30 (75)	29 (72·5)
III	7 (17·5)	7 (17·5)
IV	0	0
Treatment area		
Face	19 (47·5)	30 (75)
Face and scalp	7 (17·5)	3 (7·5)
Scalp	14 (35)	7 (17·5)
Severity of AKs		
Grade I	1 (2·5)	1 (2·5)
Grade II	39 (97·5)	39 (97·5)
Grade III	0	0
Disposition of AKs		
Localized	8 (20)	9 (22·5)
Widespread	32 (80)	31 (77·5)

VIS + wIRA, visible light plus water-filtered infrared A; PDT, photodynamic therapy; LED, light-emitting diode; AKs, actinic keratoses.

Treatment procedures

A detailed medical history was obtained. AKs were classified as follows: grade I, hardly visible, slightly palpable; grade II, easily visible and palpable; grade III, hyperkeratotic. Lesions were photographed. Each patient was assigned a specific patient number. The patient number was randomly assigned to either group 1 (VIS + wIRA PDT, n = 40 patients) or group 2 (LED PDT, n = 40 patients, Table 1).

Each AK area was pretreated by a superficial, bloodless removal of scales. A 1-mm layer of MAL cream (Metvix®; 160 mg g^{-1}, maximum 2 g per patient) was applied to each lesion and a 5-mm margin of the surrounding tissue and covered with an adhesive occlusive dressing (Tegaderm; 3M Health Care, Neuss, Germany) and a light-tight dressing (aluminium foil, gauze compress). After 3 h, the cream was removed and washed off with 0·9% saline solution. Patients' eyes were covered with safety glasses.

For irradiation two different sources were used. The first was a broadband VIS + wIRA radiator (Hydrosun® type 505) with a 7-mm water cuvette and an orange filter OG590, which provides approximately 35% more weighted effective integral irradiance with respect to the absorption spectrum of protoporphyin IX (PpIX) compared with the more common orange filter BTE 595. The water-filtered spectrum was in the range 580–1400 nm without distinct peaks. The unweighted (absolute) irradiance (irrespective of the absorption spectrum of PpIX) was approximately 200 mW cm^{-2} VIS + wIRA, including approximately 50 mW cm^{-2} VIS, and the application time was 20 min, resulting in an unweighted irradiation dose of approximately 240 J cm^{-2}, including 60 J cm^{-2} VIS. The second source was a narrowband device with LEDs (Aktilite® CL 128 lamp) with a spectrum in the range of 590–660 nm, with a distinct peak at approximately 630 nm. The unweighted irradiance was approximately 75 mW cm^{-2}, the application time 8 min, and the unweighted irradiation dose approximately 37 J cm^{-2} (according to the manufacturer). Both devices were used in accordance with the manufacturers' instructions. The LED light source was equipped with a fan to cool the skin.

Treatments were performed by a certified study nurse. The investigator who later performed the clinical assessment was not involved in this phase of the study. Thirty-six patients were offered the possibility of requesting a short interruption

Table 2 Maximum pain, spray cooling, and treatment interruptions during PDT

	VIS + wIRA PDT (n = 40)		LED PDT (n = 40)	
	Group 1 A (without spray cooling; n = 17)	Group 1 B (with spray cooling; n = 23)	Group 2 A (without spray cooling; n = 19)	Group 2 B (with spray cooling; n = 21)
Median of maximum pain (VAS)	50	65	80	60
Total number of spray coolings	0	64	0	55
Median number of spray cooling per patient	0	3·5	0	3
Total number of treatment interruptions	16	0	16	0
Number (%) of patients with treatment interruptions	5 (29)	0	8 (42)	0
Total duration of treatment interruptions (s)	275	0	240	0

VIS + wIRA, visible light plus water-filtered infrared A; PDT, photodynamic therapy; LED, light-emitting diode; VAS, visual analogue scale [0 (no pain)–100 mm (extremely painful)].

of the PDT in case of intolerable pain, but were not offered a cold liquid spray (Table 2). The other 44 patients were given the option of requesting a cooling spray (0·9% saline solution in a spray can) or, alternatively, a short interruption of the illumination, if the pain could no longer be tolerated. The liquid spray was only applied briefly, not continuously, in order to avoid uncontrolled light absorption. The amount of spray applied, the duration of application and the length of the interruptions were recorded. After PDT, the treated area was covered by a lightproof cap or dressing. Patients were instructed to avoid exposure to sunlight especially during the first 2 days after PDT because of photosensitivity. Moreover, patients were instructed to wear hats and use sun cream during a 2-week period thereafter.

In most previous clinical PDT studies on related questions three to eight isolated AK lesions were included and the complete clearance of each lesion was documented.[5] This evaluation is suitable to determine efficacy in isolated AK lesions, and pain levels are usually low during PDT of these isolated AKs. In daily routine work, most patients treated have multiple widespread and confluent AKs. In multiple AKs, the lesions are not really separable and countable. In these patients PDT is a first-line treatment that addresses both the clinically visible lesions and the entire area of cancerization. Therefore, estimating the global aspect of the total AK area by a visual analogue scale (VAS) and estimating the percentage of the cleared area in relation to the initial total AK area are appropriate variables of interest. In addition, for such patients pain during PDT is a major problem. Pain is typically assessed using a VAS. Thus, efficacy of therapy and pain were evaluated using a VAS. In several previous publications VASs have been evaluated for their usefulness in determining levels of pain, wound healing and cosmetic outcome as well as the degree of clinical improvement of acrosclerosis, systemic sclerosis and psoriasis.[4,6–8]

Therefore before PDT, as well as 2 weeks and 3, 6 and 12 months after the first PDT, the physicians documented the global aspect of the total AK area and the extent of erythema, scaling, crusts, indurations, erosions, ulcerations, oedema, skin atrophy, scar formation and pigmentation on a VAS [0 (nonexistent)–100 mm (extremely high)]. At the same time points, patients were asked to evaluate the intensity of pain, side-effects, treatment satisfaction and quality of life on a VAS [0 (none)–100 mm (extremely high)]. The cosmetic appearance was assessed by physicians and patients before and 2 weeks and 3, 6 and 12 months after the first PDT [VAS: 0 (extremely bad)–100 mm (extremely good)], as was the efficacy of PDT [VAS: −50 mm (extreme worsening), 0 mm (unchanged), +50 mm (extreme improvement), one of two confirmatory main variables of interest]. In total, approximately 25 variables of interest were assessed per patient and per time point of evaluation. Additionally, in order to assess further the appropriateness of the use of VAS in this study, the five-point scale-rated variable 'percentage of the cleared area in relation to the initial total AK area' (100% clearance, ≥ 75% of the total AK area cleared, ≥ 50% of the total AK area cleared, ≥ 25% of the total AK area cleared, no relevant part of the AK area cleared), which can be compared with the VAS assessment of therapy efficacy, was included. Pain levels were recorded using a VAS [0 (no pain)–100 mm (extremely painful)] by the patients before PDT and 2, 4, 6, 8, 10, 13, 15, 20, 22 and 25 min after the start of PDT. The highest value of these pain levels between 2 and 25 min – the maximum pain – was used as the other of two confirmatory main variables of interest. Patients were asked about the characteristics of the pain at 6 and 25 min after start of PDT. Both patients and investigators remained blinded until study completion.

Statistical analysis

Nonparametric methods were used both for confirmatory and descriptive statistics. Regarding the necessity of alpha error adjustment in cases of multiple testing, confirmatory analysis was focused on the clinically most important two main variables of interest, which in this study were 'maximum pain during PDT' (assessed by the patients) and 'efficacy of therapy' (assessed by the physicians).

Primary comparison was 'VIS + wIRA' vs. 'LED', secondary comparison 'without spray cooling' vs. 'with spray cooling' (performed with two-sided Mann–Whitney U-tests). This leads to an alpha error adjustment by Bonferroni–Holm with alpha* = alpha/4 for the smallest P-value (two comparisons × two variables of interest × one point of time), as only one value of 'maximum pain' exists per patient and as 'efficacy of therapy' should be tested in a hierarchical manner at 3 months, then 6 and then 12 months, only proceeding if the test ahead is significant (within such a hierarchical testing no additional alpha error adjustment is necessary).

Only as an alternative confirmatory statistical point of view, the four subgroups ('VIS + wIRA without spray cooling', 'LED without spray cooling', 'VIS + wIRA with spray cooling', 'LED with spray cooling') were compared in an overall test (Kruskal–Wallis test; if significant, with Conover–Iman tests as post-tests). This leads to an alpha error adjustment by Bonferroni–Holm with alpha* = alpha/2 for the smallest P-value (one comparison × two variables of interest × one point of time), as only one value of 'maximum pain' exists per patient and as 'efficacy of therapy' should be tested in a hierarchical manner at 3 months, then 6 and then 12 months, only proceeding if the test ahead is significant.

Descriptive analysis was performed with median, 25th and 75th percentile (interquartile range, IQR), minimum and maximum (box and whisker graphs).

Results

Study patients

Seventy-one white men and nine white women were included in the study. Patient age ranged from 56 to 85 years (median 70). Most patients had field cancerization (VIS + wIRA PDT group, 80%; LED PDT group, 78%; Table 1). The two treatment groups were almost identical with respect to demographic and baseline characteristics (Table 1). Sixty per cent of the patients had previously received other treatments for their AKs (data not shown).

No suspected unexpected serious adverse reactions were observed. Four patients did not complete the study: two patients discontinued the study due to lack of interest, and one couple missed the follow-up visits because the wife developed colon cancer and her husband became her primary carer.

Three months after the first PDT the clinical results were assessed. In those cases in which an incomplete healing was observed, a second PDT was performed. In the VIS + wIRA PDT group and the LED PDT group, 13 and eight patients, respectively, required a second PDT. These comprised 12 patients treated with cold liquid spray (VIS + wIRA group, n = 8; LED group, n = 4) and nine patients without spray cooling (VIS + wIRA group, n = 5; LED group, n = 4).

No patient had taken pretreatment analgesia before either the first or second treatment.

Maximum pain during photodynamic therapy

Maximum pain during PDT was one of the two main variables of interest. Thirty-six patients were not allowed cold liquid spray on demand. Instead, they only had the option of asking for interruptions of light exposure during PDT if the pain became intolerable. PDT had to be discontinued for a few seconds in 29% (five of 17) of the VIS + wIRA PDTs and in 42% (eight of 19) of the LED PDTs. In this group without spray cooling, VIS + wIRA PDT was markedly and significantly less painful than LED PDT [median of maximum pain 50 vs. 80, IQR 25–82·5 vs. 60–80, median difference −25, 95% confidence interval −40 to 0 (Fig. 1); Kruskal–Wallis test: P = 0·0237 (≤ 0·025), with Conover–Iman test as post-test: P = 0·025].

Forty-four patients received spray cooling (0·9% saline solution) on demand. No relevant difference in the median score of maximum pain was seen between the VIS + wIRA PDT group with spray cooling and the LED PDT group with spray cooling (median 65 vs. 60; Fig. 1). In both groups, no patients requested treatment interruption (Table 2).

Pain after photodynamic therapy

Pain decreased immediately after completion of PDT irradiation in both groups, irrespective of spray cooling. The duration of pain during the first 20 h following treatment was longer after LED PDT (VAS, median 51) than with VIS + wIRA PDT (VAS, median 0). In the LED group with cooling, the pain persisted the longest (median 100). In addition, the retrospective assessment of the severity of pain revealed higher levels of pain sensation in the LED PDT groups (without cooling, median 30; with cooling, median 10) compared

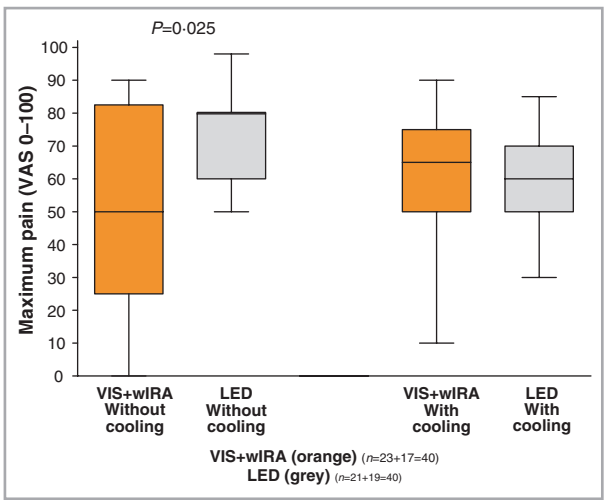

Fig 1. Maximum pain levels between 2 and 25 min after the start of visible light plus water-filtered infrared A (VIS + wIRA) photodynamic therapy (PDT) or light-emitting diode (LED) PDT, assessed using a visual analogue scale (VAS): 0 (no pain)–100 mm (extremely painful).

with the VIS + wIRA groups (without and with cooling, median 0).

Adverse events

Both VIS + wIRA PDT and LED PDT showed mild to moderate adverse events. The reported local reactions were erythema, crusting, skin scaling, blisters, pustules, pruritus, headache and dizziness (Table 3). More blisters and pustules were observed in the LED PDT groups compared with the VIS + wIRA groups. In the two treatment groups LED PDT and VIS + wIRA PDT without spray cooling, crusting and in particular scaling of the skin were more frequent compared with the groups with cold liquid spray. No serious adverse events related to treatment were observed.

Efficacy of therapy

The efficacy of therapy was documented on a VAS (−50 mm, extreme worsening; 0 mm, unchanged; + 50 mm, extreme improvement). All patients showed a marked improvement in skin status after 2 weeks (Fig. 2a, b). After 3, 6 and 12 months, a very good efficacy of therapy was observed in all groups as assessed by both the physician (Fig. 2a) and the patients themselves (Fig. 2b).

The efficacy of therapy, assessed by the physician, as the second main variable of interest, was better in patients without spray cooling [at 3 months, $P = 0{\cdot}00022$ ($\leq 0{\cdot}0125$), median 50 vs. 45, IQR 45–50 vs. 33–48; and at 6 months, $P = 0{\cdot}0068$ ($\leq 0{\cdot}0125$), median 50 vs. 48, IQR 49–50 vs. 42–50; assessed with a VAS −50/+50 (Fig. 3a); percentage of patients with complete clearance of the total AK area at 3 months 64% vs. 47%, and at 6 months 80% vs. 56% (Table 4)] and showed no significant differences between VIS + wIRA and LED (Fig. 2a). No gender-specific differences were apparent.

The data using a five-point rating scale of therapy efficacy (Table 4) are in good accordance with the therapy efficacy assessed with a VAS (Fig. 2a). The VAS has the advantage of allowing a much greater differentiation than a five-point rating scale (all mentioned assessments done by the physician).

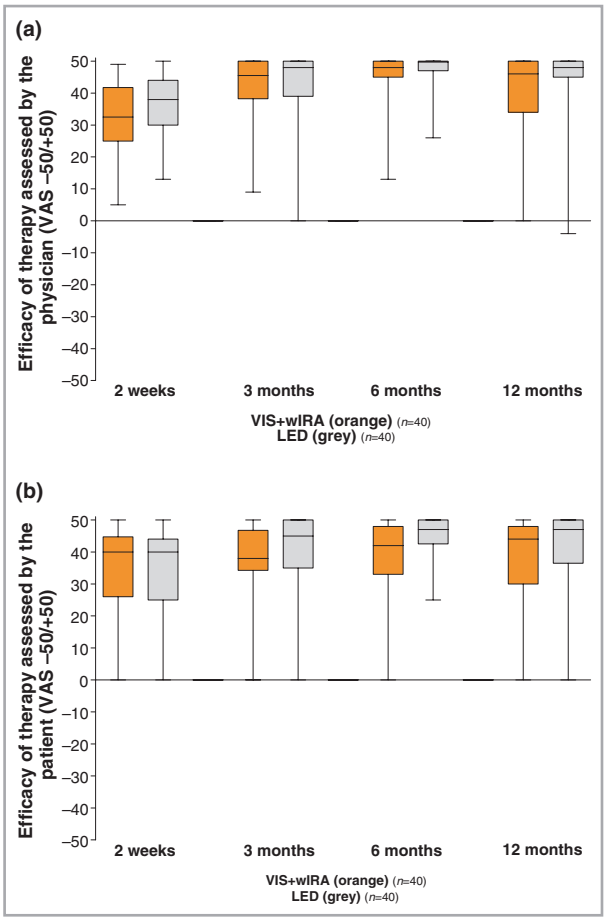

Fig 2. Efficacy of therapy at 2 weeks and 3, 6 and 12 months after visible light plus water-filtered infrared A (VIS + wIRA) photodynamic therapy (PDT) or light-emitting diode (LED) PDT, assessed by the physician (a) and the patient (b) using a visual analogue scale (VAS): −50 mm (extreme worsening), 0 mm (unchanged), + 50 mm (extreme improvement).

Table 3 Number (%) of patients reporting adverse events after treatment

	VIS + wIRA PDT (n = 40)		LED PDT (n = 40)	
	Group 1 A (without spray cooling; n = 17)	Group 1 B (with spray cooling; n = 23)	Group 2 A (without spray cooling; n = 19)	Group 2 B (with spray cooling; n = 21)
Erythema	14 (82)	17 (74)	14 (74)	18 (86)
Crusting	7 (41)	8 (35)	11 (58)	9 (43)
Skin scaling	13 (76)	10 (43)	13 (68)	8 (38)
Blisters	0	1 (4)	2 (11)	2 (10)
Pustules	0	1 (4)	3 (16)	2 (10)
Pruritus	0	0	2 (11)	0
General symptoms (e.g. headache, dizziness)	2 (12)	0	0	3 (14)

VIS + wIRA, visible light plus water-filtered infrared A; PDT, photodynamic therapy; LED, light-emitting diode.

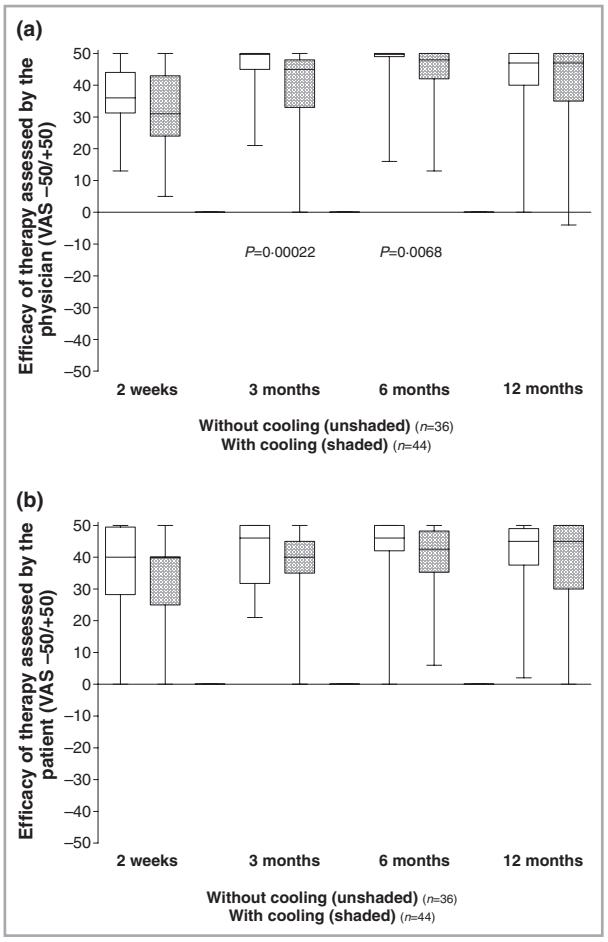

Fig 3. Efficacy of therapy – without and with the application of spray cooling during PDT – at 2 weeks and 3, 6 and 12 months after visible light plus water-filtered infrared A (VIS + wIRA) photodynamic therapy (PDT) or light-emitting diode (LED) PDT, assessed by the physician (a) and the patient (b) using a visual analogue scale (VAS): −50 mm (extreme worsening), 0 mm (unchanged), +50 mm (extreme improvement).

In addition, the efficacy of therapy assessed by the physician and the patient, both using a VAS, are in good accordance with each other: comparison of Figure 2a with 2b and comparison of Figure 3a with 3b (given that the quality of assessment of a skin-related item by a physician is higher than that by the patients[4]).

The good agreement between the different methods used in this study show that in this context the VASs used are appropriate for the assessment of the variables of interest.

Cosmetic outcome

The cosmetic outcome was also assessed using VAS [0 (extremely bad)–100 mm (extremely good)]. Already after 2 weeks, the physician and patients rated the cosmetic result as being improved. After 3, 6 and 12 months the cosmetic outcome was rated as excellent (Fig. 4). There was no apparent difference between the results of VIS + wIRA and LED.

Discussion

This clinical study was performed with the aim of comparing two light sources, both of which emit incoherent radiation, with regard to pain levels during and after PDT as well as efficacy and cosmetic outcome. Light systems with large field illumination capable of treating large areas were chosen as most of the patients had field cancerization.

The emission spectrum of the LED system consists mainly of wavelengths around 630 nm, one of the absorption bands of PpIX. Juzeniene *et al.*[9] reported a greater temperature increase and more pain in healthy human skin after exposure to light emitted by a filtered halogen lamp (CureLight1; CureLight, Gladstone, NJ, U.S.A.) compared with an LED device (CureLight2; CureLight). Moreover, superficial skin heating effects of the LED system were minimized by fan cooling the skin. The VIS + wIRA device with an OG590 filter emits wavelengths in the range of 580–1400 nm. VIS + wIRA causes minor heating of the skin surface, so that the skin temperature does not typically exceed 38–39 °C.[10,11] Moreover, wIRA has been shown to increase blood flow and tissue oxygenation, two important factors of metabolism.[4,10,11] This can potentially improve the efficacy of PDT.

Table 4 Percentage of patients with complete clearance of the total actinic keratosis (AK) area[a] and percentage of patients with at least 75% of the total AK area cleared

	3 months	6 months	12 months
Complete clearing[a]			
VIS + wIRA PDT (n = 40)	20/40 (50%)	24/39 (62%)	14/39 (36%)
LED PDT (n = 40)	23/39 (59%)	28/39 (72%)	21/37 (57%)
Without spray cooling (n = 36)	23/36 (64%)	28/35 (80%)	17/35 (49%)
With spray cooling (n = 44)	20/43 (47%)	24/43 (56%)	18/41 (44%)
At least 75% clearance			
VIS + wIRA PDT (n = 40)	36/40 (90%)	36/39 (92%)	33/39 (85%)
LED PDT (n = 40)	38/39 (97%)	38/39 (97%)	34/37 (92%)
Without spray cooling (n = 36)	35/36 (97%)	34/35 (97%)	33/35 (95%)
With spray cooling (n = 44)	39/43 (91%)	40/43 (93%)	34/41 (83%)

VIS + wIRA, visible light plus water-filtered infrared A; PDT, photodynamic therapy; LED, light-emitting diode. [a]A rigid definition of complete clearance of the AK area was used: no residual AK within the total AK area was allowed.

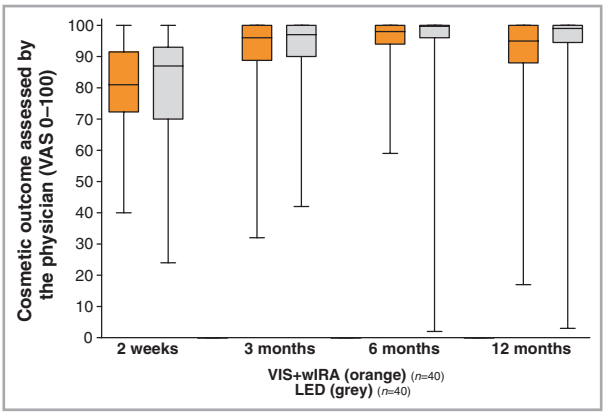

Fig 4. Cosmetic outcome at 2 weeks and 3, 6 and 12 months after visible light plus water-filtered infrared A (VIS + wIRA) photodynamic therapy (PDT) or light-emitting diode (LED) PDT, assessed by the physician using a visual analogue scale (VAS): 0 (extremely bad)–100 mm (extremely good).

Several studies focusing on the influence of different light sources with incoherent light on different aspects of PDT have been performed in recent years. In a split-face study Babilas *et al.*[12] evaluated the efficacy, painfulness, patient satisfaction and cosmesis of LED-based PDT (LEDA®; WaveLight AG, Erlangen, Germany) on the one hand and a broadband light source (PDT 1200L®; Waldmann Medizintechnik, Villingen-Schwenningen, Germany) on the other. Six months after PDT, no significant differences regarding patient satisfaction were documented. Pain during irradiation, assessed with a VAS, showed equal intensity in both treatment groups. Efficacy and cosmetic outcome were assessed as being excellent by both patients and physicians.[12] Similarly, using a combined *in vitro* and *in vivo* approach, Babilas *et al.*[13] detected no significant differences between an LED (OmniLux®; Waldmann Medizintechnik) and a broadband light source (PDT 1200®) with regard to efficacy and cosmetic outcome, pain inflicted and overall patient satisfaction. Comparison of variable pulsed light (VPL) MAL PDT and LED MAL PDT by the same group also revealed equally satisfactory therapeutic and cosmetic results.[14] Painful sensations, however, were less frequent and reportedly less intense with VPL PDT compared with LED PDT in this study.[14] Pain is a major problem during PDT for multiple AKs. Previous studies have reported the influence of various light sources (e.g. green vs. blue or red light), photosensitizers (e.g. 5-ALA, MAL) and treatment modalities on pain experienced during treatment. Importantly, PDT of large AK lesions (≥ 130 mm^2) is significantly more painful, especially when the skin of the head is involved.[15,16] As stated above, our cohort of patients had mostly large AKs of the head.

To reduce pain experience, various interventions have been used before, during and after PDT, e.g. topical anaesthesia, subcutaneous infiltration anaesthesia, oral analgesia, cooling (e.g. fan), sprayed water.[17,18] In two treatment groups we offered spray cooling on demand. In those patients of the present study who did not receive spray cooling, VIS + wIRA PDT was associated with markedly and significantly lower levels of maximum pain compared with LED PDT (Fig. 1). In this group, the post-PDT pain levels were also lower and the duration of pain after PDT was shorter compared with the LED PDT group. In this context, it is important to consider the fact that the light source used for LED PDT was already equipped with a fan to minimize pain. Concerning maximum pain, all other comparisons of the four therapy groups (with five other Conover–Iman tests as post-tests to the Kruskal–Wallis test) revealed no other significant differences and – with the exception of a trend that LED PDT without cooling showed higher levels of maximum pain than LED PDT with cooling – no other trends.

As we observed – within all four therapy groups – the lowest median of maximum pain and the lowest retrospectively assessed pain duration in the group with VIS + wIRA PDT without spray cooling, and as the efficacy of therapy at 3 and 6 months was clearly and significantly better in those patients who did not receive spray cooling, spray cooling with liquids (e.g. 0·9% saline solution) is not to be recommended during PDT, at least with these two light sources.

The effectiveness of wIRA in reducing pain has been seen in a variety of dermal and nondermal indications and by different study groups.[10] Hartel *et al.*,[4] in a randomized controlled study with 111 patients, showed that VIS + wIRA significantly improved wound healing and decreased postoperative pain and consumption of analgesics (by between 57% and 70%) compared with the control group treated with VIS alone. Possible mechanisms which may be involved in the wIRA-related pain reduction (e.g. increased tissue oxygen partial pressure, temperature, perfusion and metabolism, possible direct effect on pain reception) have previously been described.[4,19] A decrease in pain in the present study was therefore not surprising, although it is not clear whether the different spectra with different spectral irradiances and light doses might have contributed additionally to the wIRA component as far as the pain reduction was concerned. Further clinical trials are under way to determine the mechanisms responsible for the differences in pain levels during PDT with and without wIRA.

In the present study VIS + wIRA was less painful than LED for PDT of multiple AKs without spray cooling. Whether this also applies during PDT of other diseases with these devices remains to be seen.

Therapeutic results were favourable in all groups after 2 weeks and 3, 6 and 12 months, with no significant differences between VIS + wIRA and LED. The good overall results after 3 months were in line with those reported by other groups.[20–23] However, most of these studies did not document the long-term follow-up of patients after 6 and 12 months. Interestingly, the efficacy of therapy at 3 months and the long-term (6 months) efficacy were significantly better in those patients who did not receive spray cooling in our study.

Between 9 and 12 months after PDT, new AKs appeared at the site of the initial treatment in a subset of patients in both

groups (VIS + wIRA and LED), tending to a slightly less favourable efficacy after 12 months. Such lesions have also been described by other authors.[2,17,24]

The cosmetic outcome 3, 6 and 12 months after PDT was excellent in all groups. This is in accordance with results reported in the literature.[2,3]

In most previous studies, single, localized AKs of the face and scalp were treated.[20–22] In clinical practice, however, most patients have extended, often confluent AKs (field cancerization). Therefore, our study cohort consisted mostly of patients with field cancerization of the face and hairless scalp. We found a high degree of efficacy with almost complete removal of the AKs with either VIS + wIRA PDT or LED PDT. These data are in line with the results obtained by Szeimies *et al.*,[25] who showed that topical PDT using an LED is an effective treatment for multiple AKs.

In a controlled study on the effectiveness of 5-ALA PDT, Piacquadio *et al.*[26] found erythema of the skin immediately after irradiation in 99% of the patients. Erythema was still visible 1 week (83%) and 4 weeks after PDT (57%). In addition, oedema (38% after 24 h, 5% after 1 week), crusts (49%), itching (30%), scaling (31%) and blistering (1%) were observed. The authors also did not detect any alterations of pigmentation or scarring. Clark *et al.*[27] described alterations in pigmentation in 10 of 483 lesions (2%) with various light sources [Waldmann PDT 1200®, CureLight®, xenon lamp or Diomed® diode laser (Diomed, Queensbury, NY, U.S.A.)]. Superficial scarring and a case of ulceration were only seen following treatment using a diode laser (Diomed®). Secondary bacterial or viral infections have not been reported at a significant rate. Rarely, transient milia are found.

In the present study, adverse side-effects were in the range described in the above-mentioned studies. Erythema (range 74–86% in the different treatment groups), scaling (38–76%) and crusting (35–58%) were frequent; blistering (0–11%), pustules (0–16%), pruritus (0–11%) and general symptoms (headache, dizziness: 0–14%) were infrequent. We observed no alterations of pigmentation, scarring or hair loss. Interestingly, the adverse effects in the VIS + wIRA and LED PDT groups tended to be more frequent in the subgroups without spray cooling. It can be speculated that spray cooling reduces the intensity of the PDT. Pustules occurred in five of 40 patients (12·5%) who underwent LED PDT and in only one of 40 (2·5%) with VIS + wIRA PDT.

In conclusion, MAL PDT with VIS + wIRA and MAL PDT with LED were found to be long-term effective treatment modalities for multiple AKs in the present study. The efficacy of therapy – especially at the observation points 3 and 6 months – was better for those patients who were not offered cold liquid spray for pain reduction during irradiation. Therefore, spray cooling cannot be recommended for pain reduction during MAL PDT at least with these two light sources. For those patients who were not given the option of reducing pain with a cold liquid spray, VIS + wIRA was less painful than LED for PDT of multiple AKs.

What's already known about this topic?

- The efficacy of the light-emitting diode (LED) device Aktilite® CL 128 (Galderma, Bruchsal Germany) in clearing actinic keratoses (AKs) with 5-aminolaevulinic acid and methyl aminolaevulinate (Metvix®; Galderma) photodynamic therapy (PDT) has already been examined in several studies and is well documented.
- The halogen radiator (Hydrosun® type 505; Hydrosun Medizintechnik GmbH, Müllheim Germany) has not been investigated for PDT of AKs in a larger, double-blind study so far. The visible light and water-filtered infrared A (VIS + wIRA) device is known to reduce pain in a variety of indications and to increase tissue oxygen partial pressure, temperature and metabolism, which may improve the efficacy of PDT.

What does this study add?

- First investigator-initiated, randomized, double-blind study for the comparison of these two devices in PDT of multiple AKs of the head and scalp.
- All treatments showed high efficacy with good cosmetic outcome and high patient satisfaction.
- Efficacy of treatment was better without spray cooling. VIS + wIRA PDT was less painful than LED PDT for PDT without spray cooling.

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