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A comparison of photodynamic therapy using topical methyl aminolevulinate (Metvix®) with single cycle cryotherapy in patients with actinic keratosis: a prospective, randomized study

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BACKGROUND: Actinic keratosis (AK) is a very common condition, which has the potential of progressing to squamous cell carcinoma. The present study is a prospective, randomized study comparing the lesion response, cosmetic outcome, patient satisfaction and tolerability of a new treatment modality, photodynamic therapy (PDT), using topical methyl aminolevulinate (Metvix®), with the most commonly used standard therapy for AK, cryotherapy.

METHODS: A total of 204 patients with clinically diagnosed AK were randomized to either cryotherapy or PDT. The PDT patients were further assigned to an active or placebo group in a random, double-blind manner. Cryotherapy was performed using liquid nitrogen spray in a single freeze–thaw cycle. PDT was performed using 160 mg/g methyl aminolevulinate cream or placebo, a 3-hour application time, red light (570–670 nm) and a total light dose of 75 J/cm^2. PDT was repeated after 7 days. Two sessions of PDT were undertaken, as a previous study had shown a single session had similar efficacy to cryotherapy. Lesion response was assessed clinically after 3 months (complete response or non-complete response).

RESULTS: The lesion response rate was 91% in the methyl aminolevulinate PDT group, 68% in the cryotherapy group and 30% in the placebo PDT group. Methyl aminolevulinate PDT was statistically significantly better than both cryotherapy and placebo PDT in terms of response rates and cosmetic outcome. Most patients preferred PDT to other treatments.

CONCLUSIONS: PDT with methyl aminolevulinate is an excellent treatment option, particularly for patients with widespread damage or AK lesions in cosmetically sensitive areas. (*J Dermatol Treat* (2003) **14:** 99–106)

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Introduction

Actinic keratosis (AK) is the most frequent premalignant skin condition affecting the caucasian population. It has been estimated that 60% of predisposed individuals older than 40 years will have at least one AK.[1,2] Since at least 40% of metastatic squamous cell carcinoma (SCC) begin as AK,[3] it is imperative that the treatment of these lesions be efficacious. Today, both family practitioners and dermatologists treat AKs using a wide variety of therapies that have been documented more or less haphazardly with very few solid benchmarking studies available for comparison. An example of this is cryotherapy, where there are, to our knowledge, no published, prospective randomized clinical trials

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demonstrating the outcome of the method in AK, even though cryotherapy is the most commonly used treatment for AK. The true cure rates and side effect profiles for other conventional therapies such as curettage, topical chemotherapy, laser or electrodesiccation have also been scantily documented.

Conventional AK therapies commonly work by indiscriminate cell destruction in the treated area, thereby affecting the surrounding skin and potentially leaving scars or hypopigmented areas. The success of these mechanical methods of tumour removal is highly dependent on the skill of the operator. New treatments for AK should be lesion selective in order to maximize cosmetic results. They should also be repeatable and easy to use (operator-independent). Photodynamic therapy (PDT) with topical application of precursors of photoactive porphyrins may offer several of these advantages, and is therefore of increasing interest for the treatment of AK.[4–6] This therapy involves the *in situ* activation of a photosensitizer by visible light, thereby causing cell death.[7] Further development has resulted in the derivative methyl aminolevulinate, which has a much higher selectivity for neoplastic cells.[8–10]

The aim of the present study was to compare the efficacy and tolerability of methyl aminolevulinate PDT in the treatment of AK lesions with that of cryotherapy and PDT using placebo cream, in a prospective, randomized, controlled clinical trial.

Materials and methods

Patients

A total of 204 individuals with the clinical diagnosis of mild-to-moderate non-pigmented AK of the face or scalp, suitable for cryotherapy, with the largest diameter of each lesion being $\geqslant 5$ mm, were randomized for this study. Skin type was classified according to Fitzpatrick as type I, II, III or IV. The overall thickness of each lesion was classified into grades 1–3[11]: 1=mild/thin (slightly palpable AK, better felt than seen); 2=moderate (moderately thick AK, easily felt); and 3=severe (very thick and/or obvious AK). Grade 3 was an exclusion criterion in this study. The number of excluded lesions (grade 3, pigmented AKs or extrafacial sites) were not recorded.

All patients were given verbal and written information of the nature of the study, and signed informed consent was obtained prior to entry into the study and randomization. The study was approved by the relevant independent ethics committees, and by the Australian health authorities. The study was conducted in compliance with the requirements of the International Conference of Harmonization Guideline for Good Clinical Practice, January 1997.

Study design

The study was a randomized, reference- and placebo-controlled, parallel group multicentre study comparing the efficacy and tolerability of PDT using methyl aminolevulinate cream, conventional cryotherapy and PDT using placebo cream in the treatment of AK lesions. The study was open with regard to PDT versus cryotherapy and double-blind with regard to methyl aminolevulinate versus placebo PDT. Randomization was performed per patient for each treatment option, and stratified by centre for the nine study centres in Australia. Randomization concealment was achieved by having identically packaged Metvix and placebo creams in sequentially numbered packages for all patients. Once a patient entered the trial a sealed envelope containing the allocation to cryotherapy or PDT was opened. The cream allocated to patients in the cryotherapy group was destroyed at the end of the trial. The distribution of patients between treatment groups is shown in Table I. The four patients withdrawn from the study have been excluded from this table. The total study duration was at least 3 months, comprising a run-in period of up to 2 weeks, one (cryotherapy) or two treatment sessions (PDT) with an interval of 1 week, and a 3-month follow-up period. No specific interval was designated between any previous therapy for AK and the study treatment. However, lesions had to be suitable for cryotherapy, which would have excluded recently treated lesions. All study treatments were performed in the period from March to August, the Australian autumn and winter seasons.

Treatment procedure

The patients were randomized either to cryotherapy or PDT. Cryotherapy was performed in a manner consistent with each clinician's usual clinical practice. Apart from outlining with a marking pen, AK lesions were not prepared prior to cryosurgery. Any liquid nitrogen spray application unit available at the treatment centres was considered suitable for use in the study. The spray technique was varied so that a uniform freezing of the lesion with a 1–2 mm rim of frozen tissue beyond the marked outline could be achieved. The cryosurgery unit and nozzle size used at each centre was the same for every patient at that centre. A single timed freeze–thaw cycle[12] was used with no exact freeze time specified in the protocol, allowing clinicians to use their locally accepted regimen. The freeze time was measured as the time from the formation of an ice-ball to the commencement of thawing. The cryotherapy unit was activated during this time period to ensure the lesion and the surrounding normal skin remained frozen. Lesions with a mean diameter of <10 mm received a mean freeze time of $0{:}12 \pm 0{:}13$ s, 10–20 mm lesions a $0{:}16 \pm 0{:}15$ s freeze, and >20 mm $0{:}26 \pm 0{:}11$ s.

Within the PDT group, patients were blindly allocated

	Active PDT (n=88)	Cryotherapy (n=89)	Placebo PDT (n=23)
Age (years)			
Mean (range)	64 (33–86)	65 (38–86)	66 (49–89)
Sex			
Male	49 (56%)	54 (61%)	16 (70%)
Female	39 (44%)	35 (39%)	7 (30%)
No. (%) of patients per Fitzpatrick skin type			
I	32 (36%)	30 (34%)	12 (52%)
II	38 (43%)	41 (46%)	6 (26%)
III	15 (17%)	17 (19%)	4 (17%)
IV	3 (3%)	1 (1%)	1 (4%)
No. (%) of lesions per patient			
1–2	48 (55%)	39 (44%)	13 (57%)
3–7	27 (31%)	31 (35%)	8 (35%)
8–28	13 (15%)	19 (21%)	2 (9%)
No. (%) of lesions per grade			
Grade 1 (AK thin)	209 (58%)	232 (55%)	35 (47%)
Grade 2 (AK moderate)	151 (42%)	189 (45%)	39 (53%)
Total no. of lesions included	360	421	74

Table I

Baseline characteristics of patients

either to active or placebo PDT. Treatment information is summarized in Table II. The active cream (Metvix®, PhotoCure ASA, Oslo, Norway) contained 160 mg/g methyl aminolevulinate, and the placebo cream contained only the colour-matched cream base. Prior to administration of the cream, scales and crusts were removed and the lesion surface was roughened using a curette in order to facilitate access of cream and light to all parts of the lesion. The cream was applied, approximately 1 mm thick, onto the lesion and 5 mm of surrounding normal tissue. After application of the cream, the area was covered by an adhesive, occlusive dressing (Tegaderm®, 3M Health Care, St Paul, MN, USA). The cream was then left on the lesion for 3 h, after which excess cream was gently removed. Illumination was performed immediately after removal of the cream, using red light (570–670 nm) with intensities ranging from 50 to 250 mW/cm^2, but always with a total dose of 75 J/cm^2. Each centre used two identical lamps (CureLight, PhotoCure ASA), so that two illumination fields with a maximum diameter of 5.5 cm each could be illuminated simultaneously. The mean exposure time needed was about 10 minutes, and a maximum of 6 treatment sites per patient was permitted. Each treatment site was carefully mapped with acetate sheets and the AKs traced with permanent markers. Anatomical landmarks were marked in addition to polaroid photography for consistency of follow-up of individual lesions. The PDT procedure was repeated 7 days after the first treatment session.

	Active PDT	Placebo PDT
Application time (h:min)	3:12±0:16	3:07±0:12
Illumination time (min:s)	9: 54±4: 02	11:00±4:17
Light intensity (mW/cm^2)	145±52	134±49
Light dose (J/cm^2)	76±8	77±5

Table II

PDT treatment information (mean±SD)

Outcome measures

Efficacy responses (lesion response rate, overall cosmetic outcome and cosmetic outcome in individual lesions) were evaluated 3 months after initial treatment. Lesion response was classified as either complete response (complete disappearance of the lesion, both visually and by palpation) or non-complete response (incomplete disappearance of the lesion). *Lesion response rate* was evaluated as the percentage of lesions that responded completely. *Overall cosmetic outcome* was assessed by investigator and patient in patients for whom 100% of the lesions had responded completely, and graded as excellent (no scarring, atrophy or induration, and no or slight occurrence of redness or change in pigmentation compared with adjacent skin), good (no scarring, atrophy or induration but moderate redness or change in pigmentation compared with adjacent skin), fair (slight to moderate occurrence of scarring, atrophy or induration) or poor (extensive occurrence of scarring, atrophy or induration). This overall evaluation was related to the worst individual cosmetic outcome for that patient. *Cosmetic outcome in individual lesions* was evaluated for each lesion that had responded completely at the 3-month visit; the occurrence of the following parameters was assessed as none, slight or obvious: hypopigmentation, hyperpigmentation, scar formation and tissue defect. *Patient satisfaction* with PDT compared with any previous treatment(s) was evaluated in the active PDT group at the 3-month follow-up visit, where

previously treated patients graded the overall experience of the study treatment as better, equal or worse compared with previous treatments.

Adverse events were either reported spontaneously by the patient or elicited through open (non-leading) questioning by the investigator. Adverse events, including the local phototoxicity reactions that normally occur after PDT, were recorded before, during and after treatment, at 2 weeks by telephone contact, and at a final examination 3 months after treatment. All adverse events were followed up until resolved or as clinically required.

Statistical methods

Lesion response rates and frequency of 'excellent' cosmetic outcome were compared among the three treatment groups using the Cochran–Mantel–Haenzel test adjusted for centres. For lesion response, an assumption of independence between lesions within patients was made.

Results

A total of 204 caucasian patients (mean age 64 years; range 33–89 years) were included and randomized in the study, whereof 200 patients with 855 AK lesions received treatment: 88 patients with active PDT, 89 with cryotherapy and 23 with placebo PDT (Figure 1). Four patients were withdrawn before treatment. The treatment groups were similar as regards age, sex, skin type, lesion grade and largest lesion diameter per patient before treatment. The placebo PDT group included a greater proportion of males, and slightly more patients with skin type I and fewer with skin type II (Table I).

All efficacy results were analysed for both the intention to treat (ITT) and per protocol (PP) populations. The results given in the text and tables are for the PP population. The results of the ITT analyses were similar to those of the PP analyses for all the efficacy parameters. We used a Wilcoxon two-sample test and tested for difference in light intensity between responders and non-responders with no significant difference between the groups ($p > 0.1$). The lesion response rate was 91% in the methyl aminolevulinate PDT group, 68% in the cryotherapy group and 30% in the placebo PDT group (Table III and Figure 2). Lesion response was statistically significantly higher for methyl aminolevulinate PDT compared with both placebo PDT ($p<0.001$) and cryotherapy ($p<0.001$). Lesion response by description and location is summarized in Table III. Typical pre- and 3-month post-treatment appearances are given in Figure 3. In the methyl aminolevulinate PDT group, lesion response rates were higher in the thin lesions than in the moderately thick lesions, whereas in the cryotherapy group the response rates were higher for the thicker lesions (Table III).

	Active PDT	Cryotherapy	Placebo PDT
Lesion grade			
Thin	161/167 (96%)	144/230 (63%)	11/30 (37%)
Moderate	106/128 (83%)	134/177 (76%)	7/31 (23%)
Lesion location			
Face	213/224 (95%)	195/279 (70%)	14/51 (27%)
Scalp	54/71 (76%)	83/128 (65%)	4/10 (40%)
Overall lesion response	267/295 (91%)	278/407 (68%)	18/61 (30%)

Table III

Lesion response by lesion thickness and location (per protocol analysis)

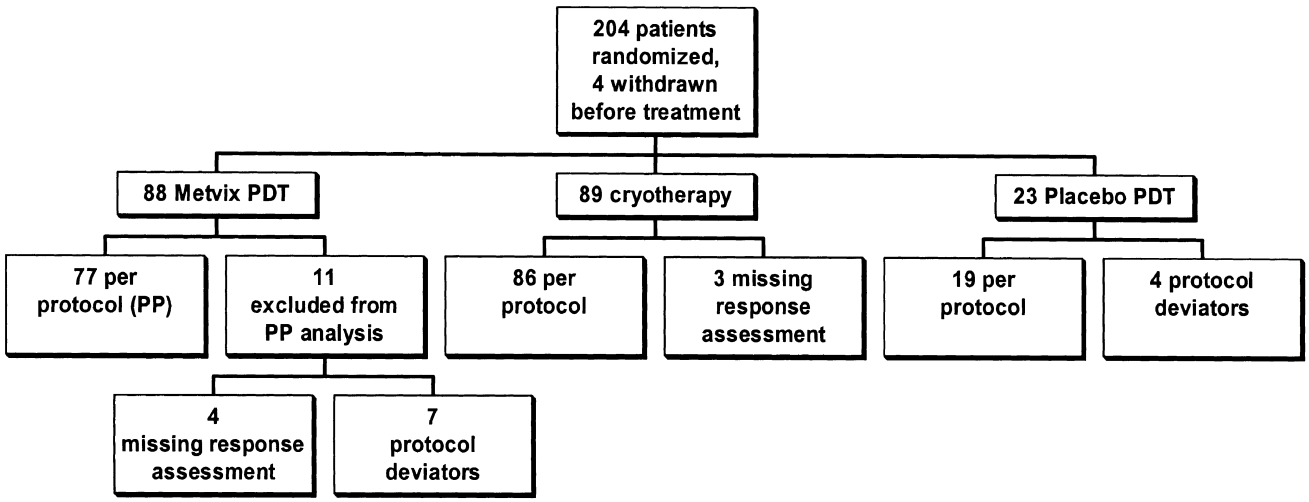

Figure 1

Flow chart of patient disposition. Protocol deviations include light parameters out of range, missing treatment sessions and incorrect treatment allocation. Missing response assessments are due to patient withdrawals or loss to follow-up.

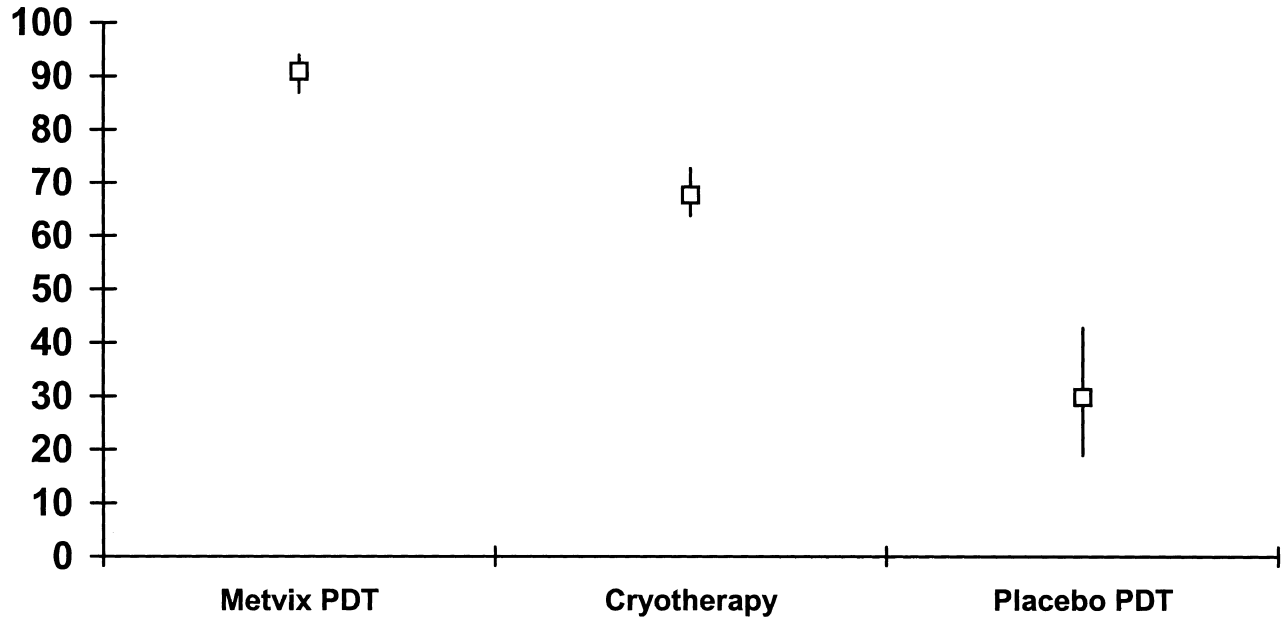

Figure 2
Lesion response, per protocol analysis (proportion estimates and 95% confidence intervals).

The overall cosmetic outcome was graded as excellent in a significantly higher proportion of the methyl aminolevulinate PDT patients compared with the cryotherapy patients (83% versus 51% as assessed by the investigator ($p<0.001$) and 76% versus 56% as assessed by the patient ($p=0.013$) (Figure 4). When grading the cosmetic outcome in individual lesions, the most common sign was hypopigmentation, present in 5% of methyl aminolevulinate-treated lesion sites, versus 29% of the lesion sites treated with cryotherapy. Hyperpigmentation, scar formation or tissue defects were present in fewer than 6% of the lesion sites in both treatment groups.

Patient satisfaction: methyl aminolevulinate PDT was rated as better than the previously given treatment in 61% of the assessments, equal in 24% and worse in 15%. Placebo PDT was rated as better than the previously given treatment (cryotherapy, surgery or 5-fluorouracil) in 21% of the assessments, equal in 14% and worse in 64%.

All safety results are reported for the ITT population, in order to reflect the safety profile of all exposed patients, regardless of whether they received per protocol treatment or whether or not they completed the study. The most common events reported were local reactions (74%). The percentage of patients experiencing at least one local adverse event was 73% after the first and 66% after the second PDT session compared with 35% after cryotherapy and 30% after the first and 27% after the second placebo PDT. Most of the local adverse events in the Metvix PDT group were of mild (48%) or moderate (40%) intensity. The majority of reported adverse reactions were expected local treatment effects that were recorded as adverse events for the purposes of the clinical trial (summarized in Table IV). The median duration was a week or less for all events. One patient in the methyl aminolevulinate PDT group discontinued the study due to the burning sensation. There were no events that suggested a systemic effect of the treatment.

Discussion

Photodynamic therapy is a new treatment for AK, and topical application of precursors of photoactive porphyrins are particularly promising. The specificity of the PDT-effect correlates with the biodistribution of the photosensitizing substance,[13] and therefore selectivity of the drug for the diseased cells is crucial. In this study, the aminolevulinate (ALA) ester methyl aminolevulinate was used. Studies have shown that ALA esters have improved penetration properties and lesion selectivity compared with ALA.[8–10]

Cryotherapy was chosen as the reference therapy as it is one of the most commonly employed therapies for AK.[14,15] In this study, cryotherapy was given in one freeze–thaw cycle since this reflected the standard treatment for AK used by Australian dermatologists. The recommended regime for cryotherapy of AK is a 5–15 s single freeze–thaw cycle of the lesion plus a 1 mm rim.[12] The overall response rate (68%) is lower than previously reported retrospective data,[16] but confirms the data from the only prospective randomized study on cryotherapy in AK to date.[17] In that study, a double freeze–thaw cycle (with a mean freeze time of 24±18 s) gave a

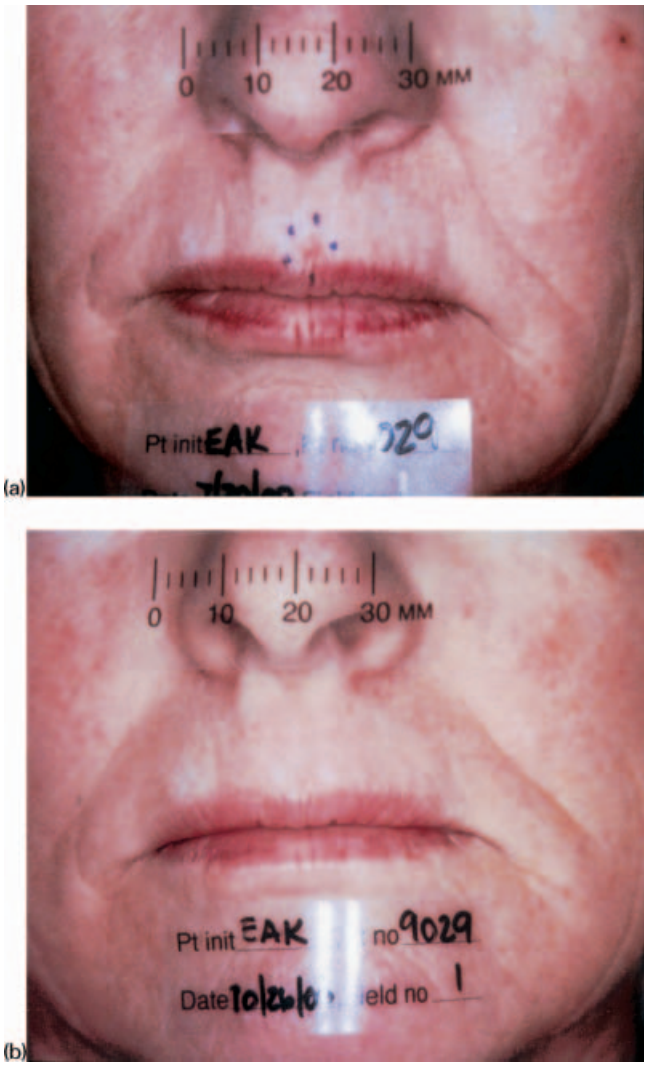

Figure 3
Typical pre-PDT (A: upper lip) and 3-month post-PDT (B: upper lip) appearances.

75% response rate for cryotherapy. These results clearly demonstrate the importance of prospectively designed and well-controlled studies to provide reliable benchmarking data on conventional treatment modalities.

A placebo group was included in order to evaluate the efficacy of methyl aminolevulinate in relation to the PDT procedure itself, i.e. preparation of the lesion with subsequent illumination, which to some extent might have an effect on the lesion. The placebo effect of 30% confirms previous reports[18] and reflects both the natural fluctuation or regression of AKs, which has been reported to be around 25%,[2] and a slight additional effect of the study procedures, particularly in the thin lesions.

Photodynamic therapy was given in two sessions 1 week apart in this study to further explore the results from an earlier study, with a relatively small number of AK patients, suggesting that re-treatment with PDT using ALA can be used to achieve higher response rates.[4] The results of this study show that the response rate is indeed improved, from the previously reported 69% complete response with single-session treatment[17] to 91% with the double-session treatment. It seems likely that the double-session PDT used in this study represents an over-treatment, since more than two-thirds of the lesions could have been cured with only one session. In the future, it may be recommended to perform one PDT session, and re-treat any lesions that do not show adequate response. This needs to be studied further.

The subgroup of lesions that had the highest benefit from the active PDT treatment was the thin facial lesions, with a lesion response rate of 97% and excellent cosmetic outcome. The facial lesions represent the biggest challenge in terms of cosmetic importance, and they are also the most common lesions. Scalp lesions showed a somewhat poorer response, both to PDT and to cryotherapy (76% and 65% respectively). Interestingly, cryotherapy was more efficacious in moderately thick lesions than in thin lesions (63% versus 76% respectively), probably because the freezing times were longer in the thicker lesions. In all, 22% of moderate lesions received a freeze time of <5 s and 39% >20 s, while for thin lesions, 35% received less than a 5 s freeze and 21% >20 s.

As expected, methyl aminolevulinate PDT was associated with a higher incidence of local reactions such as a burning sensation and erythema than the cryotherapy group. However, the duration of these events was short, and only 12% were graded as severe. Further, the actual discomfort for the patients does not seem to have been worse for the patients treated with methyl aminolevulinate PDT since methyl aminolevulinate PDT was rated as better than both surgery and cryotherapy by two-thirds of patients. We assume this is due to the relatively minor degree of discomfort, the short duration, and the expected nature of the adverse events that were directly attributable PDT effects rather than an adverse reaction.

Treatment using methyl aminolevulinate PDT is a technique that is relatively simple and quick for any dermatologist. Lesion preparation only involves superficial curettage to remove scale, application of the cream and coverage with an occlusive dressing. The patient can then leave, returning 3 h later for removal of the cream and then a 10 min illumination, before heading home. Multiple lesions may be treated simultaneously within a single illumination field. Calibration of the CureLight takes less than 1 min.

In conclusion, this randomized, reference- and placebo-controlled parallel group, multicentre study showed methyl aminolevulinate photodynamic therapy to be superior to both cryotherapy and placebo PDT in terms of lesion response as well as cosmetic outcome. The adverse reactions associated with the treatment were mostly mild or moderate local reactions of short duration. These results show that PDT with methyl aminolevulinate

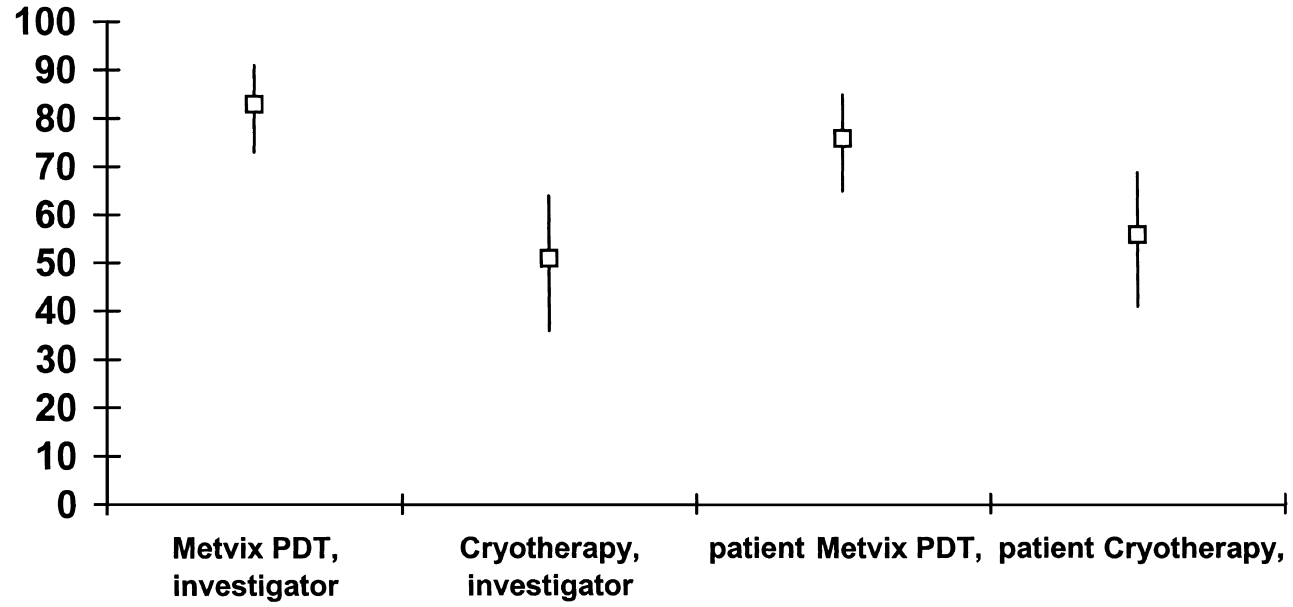

Figure 4
Percentage of patients with excellent cosmetic outcome (proportion estimates and 95% confidence intervals).

Adverse event	No. (%)
Burning sensation, stinging, painful skin	81 (46.0)
Erythema	42 (23.9)
Oedema	15 (8.5)
Skin peeling	10 (5.7)
Skin bleeding	9 (5.1)
Blisters	6 (3.4)
Itching	9 (5.1)
Crusting	4 (2.3)

Table IV
Common adverse events seen with methyl aminolevulinate PDT

is an excellent treatment option, particularly for patients with widespread actinic damage or AK lesions in cosmetically sensitive areas.

Acknowledgements

The authors have no conflicts of interest to declare.

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