Photodynamic therapy with 5-aminolaevulinic acid or placebo for recalcitrant foot and hand warts: randomised double-blind trial

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Summary

Background Photodynamic therapy (PDT) with topical 5-aminolaevulinic acid (ALA) followed by irradiation with incoherent light (ALA-PDT) for recalcitrant warts have had beneficial results. Therefore, we undertook a randomised, parallel, double-blind clinical trial of ALA-PDT versus placebo-PDT for recalcitrant foot and hand warts.

Methods Recalcitrant foot and hand warts were randomly assigned to six repetitive ALA-PDT or placebo-PDT interventions combined with standard treatment encompassing paring followed by a keratolytic (Verucid). Standardised photographs of each wart were taken before, during (week 7) and after treatment (weeks 14 and 18). The area of each wart compared with entry area was the primary outcome variable, measured from photographs by an evaluator unaware of treatment allocation for intervention. Pain intensity immediately and 24 h after each intervention was assessed by a five-point scale.

Findings A total of 232 foot and hand warts in 45 patients were entered into the trial: 117 warts were allocated to ALA-PDT and 115 warts to placebo-PDT. In week 14, the median relative reduction in wart area was 98% in the ALA-PDT group (interquartile range 100%, 55%) versus 52% (100%, 0) in the placebo group (p=0·0006). In week 18, the median relative reduction in wart area was 100% in the ALA-PDT group (100%, 57%) versus 71% (100%,0) in the placebo-PDT arm (p=0·008). Both the number of vanishing warts and the difference in relative wart area of persisting warts at week 14 and 18 were significant (p<0·05) in favour of ALA-PDT. Significantly more ALA-PDT warts were graded at a higher pain intensity after treatment than placebo-PDT warts.

Interpretation ALA-PDT is superior to placebo-PDT when both wart area and number of vanishing warts are considered.

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Introduction

Foot and hand warts cause major cosmetic, functional and social problems and are a therapeutic challenge.[1] Treatment of warts usually takes place in general or dermatological practice. Simple treatments such as wart paints combined with paring of the warts, glutaraldehyde, and cryotherapy may cure up to 70% of common hand and foot warts within 3 months.[2,3] Warts resistant to these simple "treatments" are usually dealt with by an assortment of treatments ranging from cimetidine to lasers. However, some warts remain. Patients with recalcitrant warts are frequently referred to secondary dermatological outpatient clinics, where the same interventions are reapplied due to lack of therapeutic alternatives.

Photodynamic therapy (PDT) with topical 5-aminolaevulinic acid (ALA) followed by irradiation with red light (ALA-PDT) is a well-known treatment for non-hypertrophic actinic keratoses and superficial basal-cell carcinomas. Cure rates of 90–100% have been reported in uncontrolled studies.[4,5] Only one published randomised clinical trial comparing ALA-PDT and cryotherapy for Bowen disease has shown the same cure rate after ALA-PDT as after cryotherapy, although adverse events such as infection, healing time, and scarring favoured ALA-PDT overall.[6] The use of ALA-PDT for viral infections such as herpes simplex, molluscum contagiosum, and verrucae vulgaris has been suggested.[7]

Encouraged by our preliminary positive uncontrolled observations for efficacy of ALA-PDT for recalcitrant warts,[8,9] we did a randomised, parallel, double-blind clinical trial to test ALA-PDT versus placebo-PDT for recalcitrant foot and hand warts.

Methods

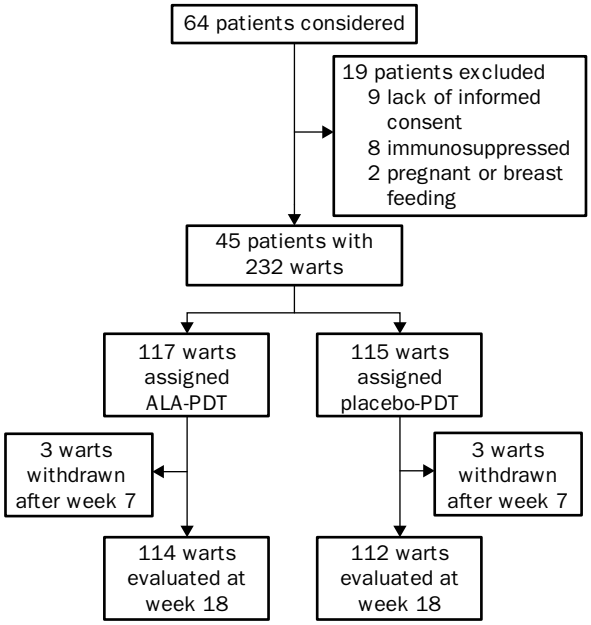
Patients

Consecutive patients with recalcitrant (in our study defined as treatment in vain by any method for more than 3 months) foot and hand warts, excluding mosaic warts, referred to the outpatient clinic of the Department of Dermatology, Bispebjerg University Hospital, Denmark, were considered eligible for this trial. Exclusion criteria were lack of informed consent, immunosuppressive therapy, other reasons for immunosuppression, pregnancy, breast-feeding, and age below 18 years. The protocol was approved by the Ethics Committee of Copenhagen and Frederiksberg (09–092/98).

Treatments

When a patient agreed to participate in our trial, all warts were consecutively numbered and the treatments were allocated blindly to intervention by an independent, centralised, computer-generated block randomisation. A block size of two (unknown to the clinical investigators) was chosen, ensuring the application of both treatments for patients with more than one wart.

All warts had the horny layer pared with a scalpel by a dermatologist to visualisation of blood vessels. The warts received, under occlusive hydrocolloid dressings, either topical application of 20% ALA cream or placebo cream base that looked and smelt the same. The cream was applied in a thick layer (0·2 g/cm^2). 4 h later all warts were irradiated with a red light source (Waldmann PDT



Trial profile

1200, Waldmann-Medizin-Technik, Villingen-Schwenningen, Germany), ranging in wavelength from 590 nm to 700 nm. The warts were exposed to a fluence rate of 50 mW/cm^2 for 23 min 20 s, corresponding to a total dose of 70 J/cm^2. Multiple warts could be irradiated at the same time. The ALA-PDT and placebo-PDT interventions were repeated after 1 and 2 weeks. If the warts persisted at week 7, ALA-PDT or placebo-PDT were applied again three times at 1-week intervals. Follow-up was at 1 month (week 14) and 2 months (week 18) after the sixth and final treatment.

Patients were instructed to pare all their warts with a scalpel twice a week during the whole study period and then apply locally a keratolytic (Verucid [salicylic acid 10% and lactic acid 11%]).

Evaluations

Photographs of each consecutively numbered wart were taken by a professional photographer at entry and after 7 (just before the fourth treatment), 14 and 18 weeks. An overview photograph was taken to identify the position of the warts. Close-up photographs together with a plastic ruler were taken for wart-area evaluation. The distance, position, and light were standardised for each photograph by use of previously taken photos.

The four close-up photographs of each wart were placed in a plastic file with four pockets. The area of the wart was measured by a dermatologist unaware of treatment allocation. Wart area was measured on each of the photographs with a divider transferred to the ruler located on the same picture. The product of the longest and widest diameter from each wart photograph was considered the wart area. Intraobserver variation was estimated on a random sample of 22 photographs which showed that 90% of the measurements varied by 2 mm or less.

Efficacy was measured as the relative change in wart area compared with wart area at entry (primary outcome measure), number of warts that vanished, and change in wart area of persistent warts.

Adverse events were registered prospectively and patients filled in a pain questionnaire concerning pain in the individual warts immediately following PDT and 24 h later. Pain was assessed by a five-point scale.[10]

Statistical analyses

With a type-1 error of 5%, a type-2 error of 20%, and an expected cure rate in the placebo-PDT of 30%—not overlooking a minimum relevant difference in cure rate of 20%—it was calculated that 103 warts per intervention arm were needed.

All data were analysed with SAS (version 6.12). Only blinded intention-to-treat analyses were done. The relative change in wart area was analysed with Wilcoxon rank-sum test, the number of vanishing warts was analysed by the χ^2 test, and the change in relative area of warts that persisted was analysed by two-way ANOVA with treatments and patients as prognostic factors. The interaction between duration of warts before entry and wart area at entry on one hand and intervention on the other was analysed by Cox proportional-hazards regression analysis. The hazard rate ratios of the Cox analyses are expressed as exp (β). Pain intensity was analysed by the Mann-Whitney test. $p<0.05$ was regarded as significant.

	ALA-PDT (n=117)	Placebo-PDT (n=115)
Median (range) wart size (mm^2) at entry	16 (2–525)	24 (2–510)
Foot warts	93 (79%)	95 (83%)
Hand warts	24 (21%)	20 (17%)

Mean number (range) of warts per patient=5 (1–19); 6 (13%) had hand warts; 8 (18%) had hand and foot warts; 31 (69%) had foot warts.

Table 1: **Characteristics of warts at entry**

Week	ALA-PDT		Placebo-PDT		p
	Persist	Vanish	Persist	Vanish	
0	117 (100%)	0	115 (100%)	0	. .
7	98 (85%)	18 (16%)	96 (84%)	19 (17%)	0·835
14	49 (50%)	49 (50%)	64 (65%)	34 (35%)	0·030
18	50 (44%)	64 (56%)	65 (58%)	47 (42%)	0·033

Table 2: **Number (%) of persisting and vanishing warts in ALA-PDT and placebo-PDT groups**

Results

From May, 1998, to November, 1998, 45 (70%) patients out of 64 consecutive patients fulfilled our inclusion criteria and none of the exclusion criteria. 19 (42%) were men and 26 (58%) were women. Median age was 37 years (range 20–84). 43 (96%) patients were referred from private dermatology practice and two (4%) from general practice. 19 patients were excluded because of immunosuppression, pregnancy, breast-feeding, or lack of informed consent (figure).

Week number	ALA-PDT (%)	Placebo-PDT (%)	Difference (95% CI) (%)	p
Week 7				
Area of warts compared with area at entrance				
Median	−33	−12		0·07
Quartiles	(−74, 0)	(−60, 0)		
Range	(−100 to 483)	(−100 to 100)		
Area of persisting warts compared to area at entrance				
Mean change (SE)	−16·4 (6·1)	−11·2 (6·1)	−5·2 (19·4, 9·0)	NS
Week 14				
Area of warts compared with area at entrance				
Median	−98	−52		0·0006
Quartiles	(−100, −55)	(−100, 0)		
Range	(−100 to 56)	(−100 to 25)		
Area of persisting warts compared to area at entrance				
Mean change (SE)	−45·3 (5·5)	−16·7 (4·8)	−28·6 (−15·9, −41·4)	0·0001
Week 18				
Area of warts compared with area at entrance				
Median	−100	−71		0·008
Quartiles	(−100, −57)	(−100, 0)		
Range	(−100 to 56)	(−100 to 60)		
Area of persisting warts compared to area at entrance				
Mean change (SE)	−38·2 (6·3)	−20·1 (5·3)	−18·1 (−3·6, −32·6)	0·015

NS=not significant.

Table 3: **Relative change in wart area and area of persisting warts compared with area at entry (%) at week 7, 14, and 18**

Intervention number	ALA-PDT					Placebo-PDT					p
	No	Light	Moderate	Severe	Unbearable	No	Light	Moderate	Severe	Unbearable	
Pain immediately after light exposure											
1	43	28	13	15	2	71	19	8	2	..	0·001
2	36	11	21	26	5	68	13	5	13	2	0·001
3	23	21	36	15	6	56	21	19	4	..	0·001
4	59	15	20	4	2	76	16	5	0	2	0·028
5	55	13	21	7	4	81	9	9	2	..	0·002
6	54	20	10	12	4	80	14	6	..	..	0·003
Pain 24 h after light exposure											
1	67	17	15	2	..	81	10	8	2	..	0·078
2	56	16	18	5	5	81	6	8	5	..	0·003
3	50	23	21	4	2	75	15	7	4	..	0·008
4	76	19	6	0	..	84	13	2	2	..	0·32
5	77	13	5	5	5	86	7	5	2	..	0·21
6	68	20	2	10	..	96	4	..	..	..	0·001

Figures are rounded.

Table 4: **Pain assessed by a five-point scale of individual warts (%) immediately and 24 h after each of six interventions**

Entry characteristics of the patients and warts of the two intervention groups, which were similar, are shown in table 1. The median duration of warts at entry was 55 months (5–240). The patients had received wart treatment for a median time of 36 months (range 5–240 months). The groups were similar in regard to prevalence of foot warts (79% *vs* 83%) and median wart areas (16 mm^2 *vs* 24 mm^2). There was no significant difference between entrance area in the two interventions arms (p=0·15). Compliance with treatment was excellent. Two patients dropped out of the trial after week 7. One patient with three warts treated by ALA and two by placebo did not want to continue because of pain. The other patient who dropped out had one placebo wart and did not want to continue after week 7 because of lack of time. Another patient with seven warts treated by ALA and seven by placebo deviated from the planned trial design because she could not endure light treatment for more than 5 min in each of the six treatments. However, she took part in all treatments and follow-ups. 5 patients with a total of 29 warts had no follow-up at week 14 due to reasons unrelated to the trial. Six warts treated by ALA and four by placebo were treated three times only because they were cured at week 7. The remaining warts were all treated six times.

The number of vanished warts was significantly (p<0·05) higher in the ALA-PDT arm compared with the placebo-PDT arm at week 14 and 18, but not at week 7 (table 2).

Table 3 shows the distribution of the relative change in wart area at each follow-up compared with the wart area at entry. The wart area decreased significantly in the ALA-PDT-treated warts compared with the placebo-PDT-treated warts at week 14 (median difference=46%, p=0·0006) and at week 18 (29%, p=0·008), but at week 7 (21%) no significant difference was observed.

Among the warts that did not vanish at weeks 7, 14, and 18, the relative reduction of wart area compared with entry area was significantly higher in the ALA-PDT arm compared with the placebo-PDT arm at week 14 (p<0·0001) and week 18 (p=0·015, table 3).

Cox regression analyses confirmed the therapeutic efficacy of ALA-PDT versus placebo-PDT (exp [β]=0·63 [95% CI 0·42–0·97], p=0·034). No significant effect on intervention efficacy was observed by including wart area at entry (0·64 [0·42–0·98], p=0·041) or wart area at entry and duration of warts at entry (0·64 [0·42–0·98], p=0·042) into the analyses. Wart size at entry (increments of 1 mm) significantly determined the probability of cure (0·95 [0·90–1·00], p=0·043), but duration of warts had no significant effect on cure rate (0·81 [0·61–1·07], p=0·133).

No local or systemic adverse events occurred in any patient, apart from pain. Patients were asked to report level of pain immediately and 24 h after each PDT intervention for up to the first four warts treated. Immediately after each treatment the pain intensity was significantly higher in the ALA-PDT group than in the placebo-PDT group. 24 h after exposure to light the pain intensity was still significantly higher in the ALA-PDT warts at the second, third and sixth treatment (table 4).

Discussion

This trial shows that ALA-PDT is better than placebo-PDT in reducing the number and area of recalcitrant foot and hand warts when the interventions were combined with regular paring followed by a topical keratolytic. However, ALA-PDT was associated with more pain, especially in the hours after the intervention.

Selective accumulation of Protoporphyrin IX (PpIX) after topical application of ALA in human-papillomavirus (HPV) infections as condylomata compared with normal surrounding skin—as well as successful treatment of condylomata with ALA-PDT described in uncontrolled reports—have opened a potential for ALA-PDT treatment of lesions caused by HPV.[11–13] This randomised trial confirms our results of uncontrolled observations in smaller patient series with warts.[8,9] We could not find any interaction between intervention efficacy of ALA-PDT and duration and area of warts at entry. The last PDT intervention in this study was done at week 9 and the last follow-up at week 18. No vanished warts recurred. From a previous uncontrolled study no recurrences were seen 12 months after warts had vanished.[9]

HPV infection is common, but the exact frequency is often underestimated and not well recorded. HPV can present on skin as foot and hand, plane and genital warts. The prevalence of common plane and plantar warts among Australian school students was 22% and almost 40% of these did not know they had warts.[14] On a single predetermined day in 1978 in Denmark all dermatologists and a random sample of general practitioners recorded that 18% of the consultations in dermatological practice, 18% of dermatological hospital outpatient clinic consultations, and 8% of skin-related consultations in general practice were about warts.[15] 62% were foot warts, 26% hand warts, 6% both hand and foot warts, 2% plane, and 4% warts located on other locations including the genital area.

When ALA penetrates the altered stratum corneum of abnormal skin it is absorbed in the keratinocytes and is converted enzymatically into the endogenous photosensitiser PpIX. Illumination of cells containing PpIX with light of appropriate wavelength releases cytotoxic

radicals. A wide range of light sources and doses has been reported effective in ALA-PDT.[16–18] We chose a commercial available light source for PDT emitting wavelengths from 590 nm to 700 nm specifically to include the absorption peaks of PpIX at 630 nm and 690 nm and at the same time excite possible photoproducts generated during the illumination. We decided to use a light dose that has often been reported effective in tumour studies.[16]

The main reasons patients gave for wanting treatment of their warts were unsightly appearance, pain, and the concern that the warts might spread.[1] Many of the patients recruited claimed that, for physical and cosmetic reasons, they could not be in a study for 4 months if they could not pare their warts, so we made paring a part of our treatment. Furthermore, regular paring followed by topical application of a keratolytic is described as an excellent treatment for common warts,[2] and, in addition, paring of the superficial horny layer enhances the penetration of ALA.

No serious local or systemic adverse events occurred in any of the patients after six ALA-PDT treatments given within 9 weeks. No scarring or skin abnormalities were seen and no disturbance of function was reported after treatment. A slight transient hyperpigmentation was observed after removal of some warts on the dorsum of the hand. ALA-PDT may, when used for treatment of non-melanoma skin cancer, induce intense pain in some patients and at certain anatomical regions. Significantly more ALA-treated warts gave severe or unbearable pain immediately after treatment with light than placebo- PDT-treated warts. Accordingly, pain should be considered a relative contraindication, particularly when treating children, who were not included in this trial.

Surprisingly, up to 13% of the placebo-treated warts gave severe pain and we saw a higher than expected wart-cure rate (42% *vs* an expected 30%) in the placebo-PDT arm of the trial. It has been reported that illumination of normal skin and tumour skin with ALA applied only induced pain in the ALA-treated tumour.[19] ALA-induced tissue PpIX can be seen with a fluorescence spectrometer giving a characteristic signal with a peak at 630 nm and a smaller peak at 690 nm. A physician, who was not involved in the clinical part of the trial, examined fluorescence. 4 h after the first cream application 38 ALA and 42 placebo warts were measured. 82% of ALA-treated warts showed the characteristic PpIX peak and, surprisingly, 60% of the placebo-treated warts showed similar but smaller peaks at 630 nm. To see if the peaks in the placebo-treated warts were due to systemic absorption of ALA, we recorded fluorescence spectra from 39 warts in 12 patients who had never been treated with ALA. 55% of these warts showed the characteristic but small PpIX peak. It is therefore less likely that the PpIX in the placebo warts had been supplemented by systemic transfer of PpIX from the ALA-treated warts. The higher than expected cure rate in the placebo-PDT treated warts could be due to naturally existing PpIX and its photodegradation products.

Our results offer promise for ALA-PDT as a safe and effective therapy for patients with recalcitrant foot and hand warts. Future randomised clinical trials should try to discover whether ALA-PDT is efficient in curing new warts, mosaic warts, and condylomata. Furthermore, it is important to find out whether an esterified lipophilic derivative of ALA, such as methyl ester ALA instead of the hydrophilic ALA used in our trial, improves the cure rate.[20]

Contributors

I-M Stender contributed to conception, design, analyses, interpreted data, drafted the paper and revised it. R Na and H Fogh made analyses and evaluated and interpreted data. C Gluud contributed to design, analyses, interpretation of data, and revision of the article. H C Wulf contributed to conception, design, interpretation of data, and revision of the article.

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