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# Is Photodynamic Therapy With Topical 5-Aminolaevulinic Acid Effective for the Treatment of Adults With Recalcitrant Hand and Foot Warts?

Nicole Hoffman
*Philadelphia College of Osteopathic Medicine*, Nicolehof@pcom.edu

# Is photodynamic therapy with topical 5-aminolaevulinic acid effective for the treatment of adults with recalcitrant hand and foot warts?

Nicole Hoffman, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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# ABSTRACT

**Objective:** The objective of this selective EBM review is to determine whether or not is photodynamic therapy with topical 5-aminolaevulinic acid effective for the treatment of adults with recalcitrant hand and foot warts.

**Study Design:** Systemic review of 3 English language primary studies, published between 1999-2007.

**Data Sources:** Two randomized controlled trials (RCTs) and one prospective, single-arm, phase II study published on/after 1999 comparing treatment of recalcitrant hand and foot warts before and after use of photodynamic therapy with topical 5-ALA were obtained using PubMed.

**Outcomes Measured:** Incidence of disappearance of recalcitrant hand and foot warts was the primary outcome measured, measured by Wilcoxon rank-sum test, $Chi^2$ test, 2 way ANOVA, measured by a ruler, Fischer's exact test for two group comparison, and Cox proportional-Hazards.

**Results:** Pain, skin pigmentation change, and phototoxic reactions were reported adverse events or side effects in some of the studies. Stender, Lock-Anderson and co-authors showed a statistically significant reduction in the frequency of warts, with a NNT of 2. Stender, Na and co-authors also showed a statistically significant reduction, with a NNT of 8. In a prospective study by Wang and co-authors 42% of patients showed complete remission of their recalcitrant hand and foot warts.

**Conclusion:** There was a significant reduction in the number of recalcitrant hand and foots warts achieved versus previously proposed methods for treatment. There was a statistically significant reduction in the recalcitrant hand and foot warts in all 3 studies, with almost half of the patients showing complete remission in Wang and co-authors study and low NNT of 2 and 8 by Stender, Lock-Anderson and co-authors and Stender, Na and co-authors respectively. To start making this more of a used modality for treatment, future larger studies with more patients with recalcitrant hand and foot warts are needed to evaluate the efficiency of photodynamic therapy with topical 5-ALA.



**Key words:** recalcitrant hand/foot warts, Photodynamic therapy, topical 5-aminolaevulinic acid

INTRODUCTION

Hand and foot warts (verrucae) are small, usually tender skin growths caused most commonly by HPV type 1 that are flattened by pressure and surrounded by cornified epithelium.[1] Hand and foot warts most commonly affect children and adolescents, but can be the most bothersome in adults. This is because in children these warts tend to resolve without treatment over several months to years, but in adults they tend to persist longer usually requiring patients to seek out treatment. While there is no one exact criteria for recalcitrant warts, they are usually considered those that persist after several months of standard treatment. [1] In the Stender, Na and co-authors study recalcitrant warts were defined as warts that persisted after 3 months of any treatment.[2] In the Stender, Lock-Anderson and co-authors recalcitrant warts were defined as warts that persisted after an average of 3 years with a variety of treatment. In the Wang and co-authors study recalcitrant warts were defined as warts that persisted after 4 sessions of cryotherapy.[4] Warts are the most common viral infection of the skin, affecting 7-10% of the general population.[5] Hand and foot warts cause cosmetic, social and functional problems to the patient.[2] While there is no direct estimate of the cost of warts in the United States, it is estimated in the United Kingdom that the annual cost is $40 million. 2 million people in the United Kingdom visit their healthcare provider each year with the diagnosis of warts.[6]

Warts are usually skin colored and when palpated are rough, but can be flat and smooth. Symptoms of hand and foot warts vary with some patients being completely asymptomatic. Foot warts are more likely to be painful and patients describe feeling a “pebble” in their shoe. Most foot warts do not stick up above the surface and have a black dot. This is due to the pressure it is under when ambulating, pushing them back into the skin. Mosaic warts are plaques of clustered hand or foot warts, which are very difficult to treat.[7]

There are over 100 different HPV types and while some are more prevalent to cause hand and foot warts, any of the 100 types can result in these types of warts. Human Papilloma Virus (HPV) infects the epithelial tissues of the skin and mucus membranes. The virus replicates in differentiated epithelial cells in the upper layer of the epidermis yet the virus can be found in the basal layer as well. This causes excessive growth of cells with the clinical manifestation of the virus being the verrucae. Dissemination systemically of the virus does not occur.[9] Infection by HPV occurs through skin-to-skin contact or Koebner phenomenon; which is an isomorphic response that occurs at sites of trauma, predisposing the patient to inoculation of the virus. Although the exact incubation period is unknown, it is believed that it ranges from 1-6 months, with a latency period of up to a year or more.[8]

There is no exact indication for treatment of plantar and palmar warts and no cure-all treatment is available. Treatment is individually based and should be considered for cosmetic reasons, poor location, or when painful. Currently used methods for treatment are but not limited to topical irritants such as: salicylic acid, bichloracetic acid, and trichloroacetic acid. Destructive methods such as cryosurgery and topical and intra-lesional immunotherapy (squaric acid dibutyl ester and Candida allergen).[2,7]

The treatment options mentioned above all play a role in treating recalcitrant hand and foot warts, however there is not one cure that will work for every patient. Trying to find one treatment that is right for the patient can be time consuming for both the practitioner and patient. Using photodynamic therapy with topical 5-aminolaevulinic acid is an effective treatment for recalcitrant hand and foot warts.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not is photodynamic therapy with topical 5-aminolaevulinic acid effective for the treatment of adults with recalcitrant hand and foot warts.

METHODS

The criteria used for the selection of the 3 studies included healthy, except for the recalcitrant warts, men and women over the age of 18 with recalcitrant hand and foot warts. Interventions included photodynamic therapy with topical 5-aminolaevulinic acid. Some variations did exist between the 3 studies. 20% ASA cream and photodynamic therapy (PDT) was compared to placebo cream with PDT in one RCT.[2] In another RCT, ALA and PDT was compared to cryotherapy with liquid nitrogen as a spray.[3] In the prospective study there was no comparison group.[4] The outcomes measured in the 3 studies included the incidence of disappearance of recalcitrant hand and foot warts.

The types of studies included are 2 randomized controlled trials and one prospective, single-arm, phase II study. Stender, Lock-Anderson and co-authors study was not blinded after 4-6 weeks.[3] All articles were published in English in peer reviewed journals. Data was collected using PubMed from 1999-2007. Key words used included "recalcitrant hand/foot warts", "photodynamic therapy" and "topical 5-aminolaevulinic acid". Articles were selected based on if they were relevant to my clinical question and if the outcomes mattered to the patients (Patient Oriented Evidence that Matters, POEMs). Inclusion criteria included studies that were either RCTs or clinical trials published on/after 1999, additional criteria in Table 1. Exclusion criteria included less than 18 years old. The statistics used to evaluate patient outcomes included RBI, ABI, NNT, and p value. The demographics and characteristics of the included studies are displayed in table 1.

**Table 1: Demographics and Characteristics of included studies**

| Study | Type | # Pts | Age (yrs.) | Inclusion Criteria | Exclusion Criteria | W/D | Interventions |
|---|---|---|---|---|---|---|---|
| Stender (2000) | Double blind RCT | 45 (232 warts) | 20-84 (mean=37) | Consecutive patients with recalcitrant (treatment in vain by any method for more than 3 months) foot and hand warts referred to the outpatient clinic of the Department of Dermatology, Bispegjerg University Hospital, Denmark | Lack of informed consent, immunosuppressive therapy, other reasons for immunosuppression, pregnancy, breast-feeding, and age below 18 | 6 warts | 20% ALA cream with PDT |
| Wang (2007) | Prospective, single-arm, phase II study | 12 | 18-70 (mean=32.8) | Adult (at least 18 years of age) patients from outpatient dermatology clinics with recalcitrant viral warts (defined as warts that persisted despite four sessions of cryotherapy) were included. | Pregnancy, breast-feeding, age less than 18, immunosuppression, and a history of photosensitivity or collagen vascular disease | 0 | 5-aminolevulinic acid with PDT (red light source Waldmann PDT1200; wavelength, 590-700 nm) |
| Stender (1999) | RCT | 30 (250 warts) | 22-74 | Referred to the Department of Dermatology at the National University Hospital, in Copenhagen in late autumn 1995 and in the spring 1996. Patients had a variety of long-standing (average 3 years) and recalcitrant warts and had been treated with a variety of modalities such as: cryotherapy, caustic agents, superficial X-rays, excision, curettage and laser treatments. | None | 2 | ALA-PDT groups were irradiated with white light applied three times within 10 days (W3) (Kindermann, fluence rate 22m W/cm2 in 30 min) |

OUTCOMES MEASURED

All of the outcomes measured were POEMs related to treating recalcitrant hand and foot warts. In the study by Stender, Lock-Anderson and co-authors the outcomes were measured by wart diameter. This was accomplished by measuring with a ruler and Fischer's exact test for two group comparison.[3]

In the study by Stender, Na and co-authors the outcomes were measured by change in wart area. This was accomplished by using Wilcoxon rank-sum test. Number of vanishing warts was measured by $Chi^2$ test. Change in relative area of warts that persisted was measured by 2 way ANOVA. Duration of warts before vs. at entry was measured by Cox proportional-Hazards. Pain intensity was measured by Mann-Whitney test immediately following PDT and 24 hours later.[2]

In the study by Wang and co-authors the outcomes were measured for statistical analysis using Leming's single stage, one-sample, multiple testing procedure. Pain intensity was measured by using a five-point scale for pain.[4]

RESULTS

Three studies compared the use of photodynamic therapy with topical 5-aminolaevulinic acid to treat adults age 18 years and older with recalcitrant hand and foot warts. One was a randomized control trial: pilot study[3], one was a randomized control trial (double-blind, placebo-controlled)[2], and one was a prospective, single-arm, phase II study[4]. Pain and transient skin pigmentation change was reported in 2 of the studies with 1 study reporting temporary erythema.

Stender, Lock-Anderson, and co-authors studied 30 patients with 250 recalcitrant hand and foot warts. No patients were excluded from the study. W3 had 73 warts and was the

experimental and cryotherapy with liquid nitrogen as a spray had 50 warts. The participants warts in the experimental were given 20% ALA to the wart and 1 cm surrounding the wart and then occluded with Tegaderm that was removed 5 hours later. The warts were then irradiated with W3 at a distance of 15 cm from the wart, with a total dose of 40 J/cm$^2$. In the control group the warts were frozen for 10 seconds from the time the wart turned white, then allowed to thaw, and then the process repeated. Cryotherapy was repeated for a maximum of 4 times within 2 months. Wart remission in W3 vs. cryotherapy was significant (p=<.01). NNT was 2 which means for every 2 warts that were treated with W3 and 5-ALA 1 more person was cured than with the control treatment. This is a small value given the study. Adverse events were mild to strong burning and itching in the first few minutes following light exposure which was followed by pain.[3]

**Table 2. Analysis of Outcomes and Numbers Needed to Treat in Patients Using Photodynamic Therapy with Topical 5-ALA for Treatment of Recalcitrant Hand and Foot Warts by Stender, Lock-Anderson, et. al.**

| Study | Patients (warts) | CER | EER | RBI | ABI | NNT |
|---|---|---|---|---|---|---|
| Stender, Lock-Anderson | 30 (250 warts) | 20% | 73% | 265% | 53% | 2 |

Stender, Na, and co-authors studied 45 patients with 232 recalcitrant hand and foot warts. Participants were excluded from the study for lack of informed consent, immunosuppressive therapy, other reasons for immunosuppression, pregnancy, breast-feeding, and age below 18. 117 warts were assigned to the ALA-PDT and 115 warts to placebo-PDT for 18 weeks. All warts had the horny layer pared with a scalpel by a dermatologist to visual blood vessels and then the

warts received occlusive hydrocolloid dressings with the experimental group receiving 20% ALA cream and the control group placebo cream that visually matched and smelled the same. 4 hours later all warts were irradiated with a red light source ranging in wavelength from 590 nm to 700 nm. Warts were exposed to a fluence rate of 50 mW/cm$^2$. The ALA-PDT and placebo-PDT were repeated after 1 and 2 weeks. If warts still persisted at week 7, ALA-PDT or placebo-PDT were reapplied 3 times 1 week apart. Follow-up was at week 18 after the 6$^{th}$ treatment. The participants were told to pare their warts with a scalpel 2 times a week and then apply a kertolytic (Verucid) locally throughout the entire study. Warts were photographed and measured with a ruler by a Dermatologist unaware of the treatments the participants in the study received. The longest and widest part of the wart was recorded. On week 18, in the ALA-PDT group 64 warts (56%) vanished while only 47 (42%) vanished in the placebo-PDT. The number of vanished warts was significantly higher, p=0.033, in the ALA-PDT than the placebo-PDT at week 18. The change of wart area on week 18 compared to the start of the study decreased significantly in the ALA-PDT versus the placebo-PDT (29%, p=.008). The CI is very narrow in the ALA-PDT versus placebo PDT (95% CI=-18.1 (-3.6, -32.6)). NNT was 8 which is very small for the magnitude of the study (see table 3). The only event reported was pain and a transient hyperpigmentation after removal of warts on the dorsum of hand. Patients were asked to report the level of pain immediately after PDT and then again 24 hours after treatment. The pain was significantly higher in the ALA-PDT versus placebo-PDT.[2]

**Table 3. Analysis of Outcomes and Numbers Needed to Treat in Patients Using Photodynamic Therapy with Topical 5-ALA for Treatment of Recalcitrant Hand and Foot Warts by Stender, Na, et. al.**

| Study | Patients (warts) | CER | EER | RBI | ABI | NNT |
|---|---|---|---|---|---|---|
| Stender, Na | 45 (232 warts) | 42% | 56% | 33% | 14% | 8 |

In a prospective study by Wang and co-authors 12 patients with recalcitrant hand and foot warts were studied and if patients had more than 1 wart one was chosen for PDT while the other was given cryotherapy. Patients who were pregnant, breast-feeding, age less than 18, immunosuppression, and a history of photosensitivity or collagen vascular disease were excluded from the study. The viral warts that were selected for treatment were pared with a scalpel until blood vessels were visualized. 20% 5-ALA cream was applied to the wart plus a .5 cm around the wart. Tegaderm was applied for 4 hours and then the warts were irradiated with a red light source ranging in wavelength from 590 to 700 nm at an irradiance of 50 $mW/cm^2$ for 20 minutes. The total dose was 50 $J/cm^2$. The same evaluator saw the patients every 2 weeks and if necessary the PDT was repeated for a maximum of 4 times. Photographs were taken at entry and then every 2 weeks for 8 weeks. 42% of patients (5 patients) achieved complete remission ($p=0.34$). The P is >.05, which does question the validity of the study. Pain peaked at 24 hours and lasted for 48 hours with most patients rating the pain only a 1/5 and no patients asked to discontinue treatment because of pain.[4]

DISCUSSION

Recalcitrant hand and foot warts are a common problem that many patients are seeking treatment for from practitioners. While there are various methods for treatment such as but not

limited to cryotherapy, excision and caustic agents, a patient can still be left with a recalcitrant wart.[7] Therefore, photodynamic therapy with 5-ALA is necessary and may be the key for the treatment of these warts.

However, there are various problems to this proposed therapy. One problem faced with this treatment is the insurance coverage. While insurance companies do cover the use of PDT with 5-ALA for the treatment of other skin conditions such as: cutaneous lesions of Bowen's disease, basal cell carcinoma and refractory actinic keratosis. Unfortunately insurance companies such as Aetna and Cigna consider this an experimental treatment for warts and will not cover it. So patients end up paying out of pocket per treatment, which ends up being very costly because warts require numerous treatments before a cure is reached, which is also very time consuming for the patient.[10,11] Also, FDA does approve the use of photodynamic therapy with 5-ALA, but it is not an approved treatment for warts.[12]

There are contraindications for the use of this treatment. Some contraindications are cutaneous photosensitivity, porphyria and allergies to ALA. It is also not known if ALA is excreted through breast milk, so caution needs to be taken when prescribing this to a woman who is breastfeeding. After the application of ALA, the skin has some photosensitivity. The patient should be warned to avoid sunlight or any bright lights. This can be very tedious to the patient due to the topical application of ALA not just being a one-time use. ALA is considered pregnancy category C.[13,14]

There are limitations that exist when obtaining evidence of the effectiveness of 5-ALA and PDT in the treatment of recalcitrant hand and foot warts. The following are limitations that all 3 studies share. Each of the studies started treatment with a keratolytic and curettage before applying the 5-ALA and then using photodynamic therapy. Because of this, there is no way to

know if the high response rates are skewed due to the keratolyic and curettage, making 5-ALA and PDT look better than it actually is. Also, each study told the patients to apply the keratolytic at home. Because of this, there is no way to measure if patients actually complied with this treatment plan and these studies had to solely rely on patients being truthful. Also, a worst-case-analysis was not completed at the end of the studies to account for patients which may have affected the significance of the findings. Another limitation was pain. Pain was reported significantly higher in the ALA-PDT than the placebo-PDT immediately after treatment so blinding may have been compromised for both subjects and investigators. Also, all patients were referred from dermatology practices, which could make these patients more compliant than the general population when it comes to treatment of their recalcitrant warts.

There were also specific limitations to the study by Wang and co-authors. In this study, there was a very small sample size making it very difficult to apply this data to the general population. Also, this study solely focused on an Asian population. This makes it unknown if the Asian population experiences a different response rate or has different complications than other populations of individuals. It also makes it unknown if the results in this study can be generalized to different populations. Also the p-value reported in the study was $p=0.34$, which questions the statistical significance and validity of the study.

A limitation in the Stender, Lock-Anderson and co-authors study was there was no exclusion criteria for the population they choose to be a part of their study. This makes it hard to generalize the results to similar patients because the demographics of the patients in the study were not all given. Another limitation in this study was the at home use of a keratolytic was optional. The study never accounted for which patients chose and which patients chose not to apply the keratolytic. 3 patients were immunocompromised making the results unable to be

generalized to an entire population. Also, the trial was not blinded after 4-6 weeks. This gave both investigators and participants in the trial opportunity to skew the results. Control group had no topical cream application which could have made the study unblinded earlier than the researches anticipated.

## CONCLUSION

Photodynamic therapy with topical 5-ALA is an effective treatment for adults with recalcitrant hand and foot warts. While all 3 studies demonstrated a significant reduction in the number of recalcitrant hand and foot warts[2,3,4], further research is needed to apply the results to the general population. In future studies stricter inclusion criteria should be set for patients who failed a specific common treatment (e.g. cryotherapy), so practitioners know when to initiate 5-ALA with PDT. Also, only one study mentioned the different light sources available for photodynamic therapy, but only W3 was mentioned in this paper.[3] Further studies are needed to compare the light sources available so a conclusion can be made about which is more effective in the treatment of recalcitrant warts. Further studies are also needed to aim for FDA and insurance approval. This would make practitioners and patients more willing to try this treatment option because cost and safety concerns would not be an issue The reviewed studies show promise in the start of the research for treating recalcitrant hand and foot warts with 5-ALA and PDT.

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