

Off-label photodynamic therapy for recalcitrant facial flat warts using topical 5-aminolevulinic acid

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Abstract The facial flat wart (*verruca plana*) is one of the most common reasons for dermatology and primary care visits. Although there are many therapeutic modalities, no single therapy has been proven to be completely curative. Case reports and uncontrolled studies suggested that photodynamic therapy (PDT) with topical 5-aminolevulinic acid (ALA) can effectively treat recalcitrant facial flat warts. A total of 12 patients with recalcitrant facial flat warts were enrolled in the study. ALA gel (10 %) was applied topically to lesions and incubated for 3 h. The lesions were irradiated by an LED light of 630 ± 10 nm at dose levels of 60–100 mW/cm. Clinical assessment was conducted before and after every treatment for up to 24 weeks. Among the ten patients completing three sessions of ALA-PDT, five had complete lesions clearance, and the other five patients were significantly improved. At the 24-week follow-up, the average effective rate was 88.8 %, with no recurrences. No significant side effects were reported. A low-dose topical ALA-PDT regimen using 10 % ALA, 3 h incubation, and a red light source for three treatment sessions are suggested as the optimal scheme for the treatment of recalcitrant flat warts on the face in Chinese

patients. Superior efficacy is found in elevated or active period lesions with mild side effects.

Keywords Photodynamic therapy · 5-Aminolevulinic acid · Flat wart · Recalcitrant facial flat warts · Treatment outcome

Introduction

The flat wart is caused by human papilloma virus (HPV) types 3, 10, 28, and 41 and occurs on the faces of young people. Despite its general occurrence, the exact frequency of facial flat wart is often underestimated. A random sampling of 2491 students in Australia indicated a 2 % prevalence of *verruca plana* [1]. Although there are many therapeutic modalities, no monotherapy has been shown to achieve complete remission in every case, and numerous traditional treatments often produce obvious adverse effects and a high recurrence rate. In recent years, some clinical research has revealed that photodynamic therapy with topical 5-aminolevulinic acid can treat recalcitrant facial flat warts with good curative effect [2–4]. The mechanism of action is unclear but may be a result of specific destruction of superficial dilated capillaries in warts by selective photothermolysis of oxyhemoglobin within the microvasculature [5]. Many factors affect the efficacy of PDT, including photosensitizer concentration; solvent type; incubation time; type, dose, and time of irradiation of the light; and the area of exposed parts. Consequently, reports on the efficacy of photodynamic therapy for facial flat warts with ALA are scarce and fragmented. Therefore, we report here on 12 cases of multiple facial warts that were successfully treated with photodynamic therapy with 10 % ALA in our hospital, and we review published reports indicating that PDT with 10 % ALA seems to be a better treatment option for recalcitrant flat warts on the face.

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Materials and methods

Study design and setting

First, we retrospectively analyzed the twelve patients who were treated with ALA-PDT for recalcitrant facial flat warts at the Department of Dermatology of the Shanghai Changzheng Hospital during June 2012 to December 2012, and we analyzed the demographic characteristics and treatment outcomes of the clinical isolates.

To further investigate the role of ALA-PDT in the treatment of verruca plana, a review of the literature was performed to identify the relevant papers from the electronic databases of PubMed, EMBASE, China Biomedicine Database Disk, China National Knowledge Infrastructure/Chinese Academic Journals full text Database, and VIP (VIP Database for Chinese Technical Periodicals) published from January 1990 to January 2014. The Boolean search used the following key words: facial flat warts; facial verruca plana; flat wart; plane warts; facial viral warts; photodynamic therapy; aminolevulinic acid.

Patients

Twelve patients were treated with ALA-PDT for recalcitrant facial flat warts. The exclusion criteria were age less than 18 years of age, immunodeficiency, pregnancy, breastfeeding, and a history of photosensitivity, retinoid use in the last 12 months, collagen vascular disease, or other treatments within the previous 3 months. The hospital's ethics committee approved the study. Fully informed written consent was obtained from all patients before the first treatment.

Treatment procedure

Treatment involved PDT (Fudan Zhang Jiang Biomedical Corp, Shanghai, China) and an oil-in-water emulsion (stable temperature-sensitive gel freshly formulated with 10 % ALA) that was applied to lesions, which were then sealed with thin plastic wrap and covered with non-adhesive light-shielding dressings for approximately 3 h. The face was washed with saline. The lesions and at least 10 mm of surrounding healthy skin were irradiated with an LED light source (produced by WuHan YaGe Optic and electronic technique Co. LTD), mask type (length 39 cm, width 28 cm), Model LED-IB, wavelength (630 ± 10 nm), 10 cm^2 above the face, 20 min irradiation, and power ($60\text{--}100 \text{ mW/cm}^2$) with a cold wet spray 0.5 h after treatment.

Follow-up and adverse events

The patients were evaluated 2, 12, and 24 weeks after the third treatment. Photographs were taken before treatment and after

the warts cleared. Adverse effects, including pain, pruritus, redness and swelling, furfuration, and hyperpigmentation were recorded.

The treatment efficacy of each patient was assessed by determining the numerical change in lesions with the following formula: lesion clearance rate (%) = (number before treatment – number after treatment) / total untreated lesions. Responses were graded as a percentage of clearance: complete (100 %), excellent (70–100 %), good (30–70 %), and poor (<30 %). The evaluation was repeated in weeks 2, 12, and 14.

Results

Patients and lesion characteristics

A total of 12 patients were referred to the department of dermatology with recalcitrant facial warts and were treated with ALA-PDT. They received conventional therapies, such as cryotherapy, CO₂ laser, keratolytic agents, topical immunomodulators, and traditional Chinese drugs, before admission at 3 months. The mean age, lesion numbers, subtype, duration, sub-distribution, and accompanying Koebner phenomenon for the 12 patients are summarized in Table 1.

Therapeutic response and recurrences

The clinical outcomes are summarized in Table 2. Twelve patients with recalcitrant facial warts were enrolled in the study. Two patients exited the study because the treatment was ineffective. Of the ten patients completing the 3-session treatment, five had complete disappearance of their warts, and five patients showed partial clearance (greater than 50 % decrease in the wart area), with an average effective rate of 86.8 %. In the 12-week follow-up, only one recurrence was identified. At the 24-week follow-up, the average effective rate was 88.8 %, with no recurrences (Fig. 1). Two patients (i.e., patients #4 and #11) had remarkable Koebner phenomenon. After two treatments, the clearance rate of lesions was 100 %. The effective rate of ten patients with uplift lesions was 83 %. The outcome of two patients with flat lesions was not good or invalid.

All patients had varying degrees of tight skin, mild swelling, pain, and other uncomfortable sensory reactions after the first 5–10 min and at the end of ALA-PDT irradiation. Erythema and edema (83.33 %) at the treated site were the most common concomitant responses immediately after the first irradiation session. With the exception of one patient who could not tolerate the procedure, the degree of erythema and edema response was mild to moderate in most cases. These responses could be alleviated within approximately 2–3 days by local administration of a cold spray. Five patients (41.6 %) had mild to moderate desquamation at the treatment

Table 1 Characteristics of the patients and lesions of ALA-PDT in facial flat warts

No. of patients	12
Male/female	2/10
Mean age (range)	34 (29–40)
No. of lesions (range)	83.8 (55–145)
Duration (range) (months)	87 (24–168)
Stable/active/rapidly active phase (<i>n</i>)	10/1/1
Subtypes (no.)	
Normal skin color	1
Coffee color	6
Gray–brown color	5
Sub-distribution (%)	
Frontal	100
Hairline	58
Eyelid	67
Cheek	100
Nose	75
Chin	92
Neck	17
Lesion with/without height	10/2
Isomorphic reaction with/without patients	2/10

site at the first session. Slight to moderate visible hyperpigmentation occurred in all patients, which disappeared over time. At the end of follow-up (24 weeks after treatment), only three patients (25 %) had partial pigmentation. All the adverse

effects were reduced at the second treatment cycle. No infection, ulceration, scarring, or other severe adverse effects were observed.

Review of published cases of photodynamic therapy for facial flat warts with topical 5-aminolevulinic acid

According to our search criteria, 11 relevant documents were retrieved (Table 3), including 4 case reports, 6 retrospective clinical analyses, and 1 prospective clinical study. Approximately 440 cases of patients with facial warts were treated with ALA-PDT, including 61 recalcitrant cases (13.86 %).

Discussion

Verruca plana is a chronic condition that often affects young people [4]. Some trials have shown that the average reported cure rate (CR) of cutaneous warts with placebo preparations was 30 % within 10 weeks [16], and while one-half of cutaneous warts resolve spontaneously within 1 year, approximately two-thirds resolve within 2 years [17]. Watchful waiting, cryotherapy, and salicylic acid are recommended options for new warts [18]. However, some patients with recurrent facial warts of longer duration (≥ 2 years) are recalcitrant to a variety of standard treatments. Some therapies can cause enormous physical and psychological harm to patients. Recently, some newer treatments, such as topical

Table 2 Response of the lesion to ALA-PDT treatment over time

Patient no.	Mean lesion clearance rate					Categorized therapeutic responses	
	Treatment period			Follow-up period		Treatment period 6 weeks	Follow-up period 24 weeks
	2 weeks	4 weeks	6 weeks	12 weeks	24 weeks		
1	43	95	96	97	99	Excellent	Excellent
2	55	81	100	100	100	Excellent	Complete clearance
3	40	49	100	100	100	Excellent	Complete clearance
4	51	97	100	100	100	Excellent	Complete clearance
5	49	54	54	54	54	Good	Good
6	58	72	100	100	100	Good	Complete clearance
7	82	82	82	62	62	Excellent	Good
8	50	50	/	/	/	/	/
9	85	83	90	93	96	Excellent	Excellent
10	23	46	46	63	77	Good	Excellent
11	45	62	100	100	100	Excellent	Complete clearance
12	62	62	/	/	/	/	/

Fig. 1 Clinical photographs from a recalcitrant facial flat wart patient (A1–C1) treated with three sessions of 5 % ALA-PDT at baseline visit (A2–C4) and at 24-week follow-up after the last therapy (A5–C5)



immunomodulators, such as imiquimod cream, laser surgery [16], pulsed dye laser treatment [19], and photodynamic therapy, have emerged. PDT is an important option for the treatment of HPV infection-related diseases. PDT typically involves the topical application of the photosensitizer pro-drug, ALA or MAL. The side effects of this therapy are few. Numerous clinical studies have demonstrated the efficiency of PDT in the treatment of viral warts [6, 20–24] (recalcitrant or not), and several studies have shown that PDT is effective in treating plane warts [2, 4], including those on the face [3]. Several off-label applications of PDT to facial warts, especially recalcitrant cases, have been described. Regarding photosensitizer selection, most use ALA-PDT rather than MAL-PDT [25]. Some geographical differences in PDT studies exist. For instance, in China, some prospective randomized comparative experiments have been performed that compare mostly sporadic cases. In addition, differences exist in the choice of photosensitizer concentrations, with the study in China using 10 % [13], and the other countries using 20 % [2].

In 2013, three groups compared ALA-PDT treatment of flat warts to CO₂ laser, freezing, ionizing, and other traditional therapies. Wang et al. [12] and Zhang et al. [13] found that the cure rate of facial warts was significantly higher in the 10 % ALA-PDT treatment group, while the recurrence rate was significantly lower than that in the control group. This suggests that the treatment of facial warts with 10 % ALA-PDT may be better than some of the standard therapies. Chen et al. [11] found that 20 % ALA-PDT treatment of facial warts is safe and effective. To investigate the efficacy and safety of PDT with different concentrations of photosensitizer in the treatment of verruca plana, Li et al. [10] compared ALA-PDT with 5, 10, or 20 % concentrations. The results showed that the

difference between the 5 and 10 % groups and between the 10 and 20 % groups were significant. Application of 10 % ALA-PDT appeared safe and effective, while the 20 % group was more likely to exhibit pigmentation alterations and other adverse reactions. In our study, 10 % ALA-PDT was safe and effective for treatment of recalcitrant facial flat warts. After 12 weeks of treatment, the CR was 88.8 %, which was slightly lower than the 94.44 % CR reported by Lu et al. [4], higher than the 72.5 % CR reported by Li et al. [10], and higher than the CR obtained with the previously reported 20 % ALA-PDT group [10, 26]. It is worth noting that the CR rate of patient 4 and patient 11, whom lesions at the stage of Koebner phenomenon is 100%, and it is consistent with the outcome of the study of GeQiang, suggesting that ALA-PDT possible more sensitive in the outbreak of warts, or with the Koebner phenomenon. In addition, GeQiang used 5, 10, 20 % ALA in the three stages according to patient response to PDT treatment. The way to increase drug concentration at each stage may minimize the patients' adverse reactions. Considering the self-limiting nature of warts as well as medical costs and other factors, we recommend 10 % ALA-PDT as an alternative treatment option for patients with recalcitrant facial flat warts. Further clinical studies have yet to test its applicability as a conventional treatment option for facial flat warts.

In addition, our literature search identified two cases of children (≤ 16 years old) who were successfully treated with ALA-PDT [2, 9] and one case of an organ transplant patient (i.e., lung transplantation) [7]. Due to poor tolerance, cellular immune dysfunction, underlying diseases, and other factors, the facial warts in immune-compromised populations, such as HIV-positive or organ transplant patients, were often generalized, multiple, and recurrent. Some patients with long-term

Table 3 Clinical characteristics, manifestation, and treatment of patients with facial warts

Year [reference]	No. of patients	F/M	Age	Duration (months)	Photosensitizer	Incubation period (h)	Light source	Light dose	Duration (min)	Interval (d)	Session	Follow-up (months)	Adverse effects	Outcome
1999 [6]	1	ND	ND	ND	5-ALA 20 %	4–5	White light	45 J/cm ²	ND	7	3	5–17	Burning and stinging pain	ND
2003 [2]	1	0/1	13	24	5-ALA 20 %	6	500-W metal halide lamp (630–700 μm)	126 J/cm ²	20	ND	2	5	ND	Cure
2008 [3]	3	2/1	15–25	36–96	5-ALA 20 %	3	RL 633 nm	126 J/cm ²	ND	7	4–5	1–3	Itching and burning, focal erythema, and exfoliation	Cure
2010 [7]	1	0/1	64	11	5-ALA	3	RL 634 nm	37 J/cm ²	9	10	3	12	Moderate pain	Cure
2010 [4]	18	13/5	18–41	12–72	5-ALA 10 %	4	RL 635 nm	120 J/cm ²	10	15	2–3	6	Pruritus, stinging	CR 55.56 %; 10 cases cured (1 case of recurrence), 7 cases showed significant improvement, 1 case was invalid
2011 [8]	130	58/	72	13.7 ± 4.9 (7–18)	9.65 ± 5.85 (0–25–24)	5-ALA	4–5	RL 635 nm	100–150 J/cm ²	ND	10	5	3	Mild edema, itching
All 130 cases cured, 3 cases of recurrence														
2012 [9]	1	1/0	8		6-ALA	ND	ND	ND	ND	10	2	ND		Cure
2013 [10]	55	43/	12	18–53	ND	5-ALA 5, 10, and 20 %	4	RL 633 nm	113 J/cm ²	15	14	3	4	Pain, residual erythema, and persistent pigmentary alterations

The CR of the 5, 10, and 20 % ALA-PDT

Table 3 (continued)

Year [reference]	No. of patients	F/M	Age	Duration (months)	Photosensitizer	Incubation period (h)	Light source	Light dose	Duration (min)	Interval (d)	Session up (months)	Adverse effects	Outcome	
2013 [11]	60	43/	17	19–63	6–48	5-ALA 20 %	3	RL 633 nm	126 J/cm ²	ND	7	3	1	Pain, erythema
CR 98.18 %														
2013 [12]	177	105/	72	16–71	3–96	5-ALA 10 %	3	RL 635 ± 5 nm	70 mW/cm ²	20	7–10	4–5	3	Mild edema, pain
CR 94.3 %, RR 5.7 %														
2013 [13]	112	64/	48	18–60	6–60	5-ALA 10 %	3	LED	70 mW/cm ²	20	10–15	4	3	Mild edema, pain, and hyperpigmentation
CR 92 %, RR 6 %														
2014 [14]	20	14/6	19–45	ND	5-ALA 20 %	1	RL 635 ± 3 nm	128 J/cm ²	20	10	4	1	1	Mild edema, hyperpigmentation
CR 70 %														
2014 [15]	23	18/5	17–31	1–31	5-ALA 5 %	1.5	RL 633 nm	105 mW/cm ²	10	15–30	3	6	6	Mild edema, pain, and hyperpigmentation
CR 100 %														

CR cure rate, RR recurrence rate, ND no data

oral anticoagulation administration had partial clotting dysfunction, and for other patients, traditional laser therapy was not appropriate. Thus there is a need for a more safe and effective treatment method. ALA-PDT is a safe, non-invasive technique, which yields effective therapeutic results in many patients. The technique is particularly useful for slow-healing subjects and acts selectively, allowing the healthy surrounding skin to remain intact and functional [27]. The use of one or several fields of light enables treatment of many lesions at the same time, thus limiting the risk of wart spread and recurrence between sessions. In another study, a series of 31 children and adults with recalcitrant plantar warts treated with ALA-PDT attained an 88 % CR (42/48) after an average of 2.3 treatments. Younger patients had better outcomes, with 100 % clearance in all patients younger than 27, and no clearance in patients older than 45. Side effects included minor pain and itching, with one case of mild hypopigmentation [23]. We feel that ALA-PDT can be very efficient in the treatment of recalcitrant facial flat warts in immunosuppressed organ-transplanted patients and children.

During the course of our study, after the first ALA-PDT treatment, all patients had varying degrees of adverse reactions. Local erythema and edema were the most common reactions, with a rate of 83.33 %, which is in accordance with other studies [3, 8, 9, 11–13, 28, 29]. One patient withdrew because the patient could not tolerate the adverse reactions. This was not related to the severity of adverse effects, but rather due to fear of the unknown phototoxic adverse reactions. Meanwhile, we also found that after treatment, short-term pigmentation was unavoidable, with an occurrence rate of 100 %; however, at the end of follow-up (i.e., 24 weeks after treatment), its incidence decreased to 25 %, which is slightly higher than that described in other studies [10]. It is noteworthy that the severity of all adverse reactions diminished with the number of treatments, which is consistent with many other studies [10]. Therefore, adequate, informed, and timely symptomatic treatment must be emphasized. Two cases were treated during the active stage of the wart (with a positive isomorphic effect), and these patients were very sensitive to ALA-PDT treatment; the lesions cleared within two sessions, but we still recommend a third course of treatment to completely remove the hidden or latent infection and to effectively prevent recurrence [4]. Ten patients (83 %) with raised lesions were effectively treated, but treatment was ineffective in two other cases with flushed skin lesions. Whether the uplift lesions warts are an explicit factor for the outcome of ALA-PDT treatment remains to be further studied.

In conclusion, we believe that 10 % ALA-PDT can be an alternative treatment option for patients with facial warts. For immunocompromised patients and children, its efficacy and safety remain to be examined.

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Compliance with ethical standards The hospital's ethics committee approved the study. Fully informed written consent was obtained from all patients before the first treatment.

Conflict of interest The authors declare that they have no conflicts of interest.

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