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A combination of 2940-nm laser and photodynamic therapy for treatment of recalcitrant facial flat warts

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ABSTRACT

Background: Photodynamic therapy (PDT) is one of the treatment options for generalized facial flat warts, which results in elimination of virus and inhibition of proliferation of warts due to photochemical and phototoxic reactions. In this research, we attempted to evaluate the efficacy and safety profiles of a combination of 2940-nm laser and PDT for the treatment of generalized recalcitrant facial flat warts.

Methods: Retrospective analysis of the patients with recalcitrant facial warts was performed. Patients in the combined group (n = 40) were treated with a 2940-nm single spot abrasion followed by a PDT; while the PDT group (n = 40) received a PDT treatment only. The efficacy was assessed by the lesion numbers and lesion clearance rate. The effective rate was calculated with the cured and excellent response rates.

Results: The combined group showed significant improvements in the total effective rate (77.5%*vs.* 57.5%, $p = 0.0416$) and average clearance rate (81.68 ± 2.83% *vs.* 68.13 ± 3.97%, $p = 0.0068$) as compared with the PDT-only group. The degree of lesion clearance was positively correlated with the treatment times in both groups. After three months of follow-up, no relapse occurred in patients from either group. Furthermore, an accumulation of photosensitizer in the lesional areas was observed in the combined treatment group.

Conclusions: A combination of 2940-nm laser and PDT was safe and showed significantly more effect than PDT alone in treatment for recalcitrant facial flat warts, partially due to the improved uptake of photosensitizer after 2940-nm laser induced skin abrasion.

1. Introduction

Flat warts are caused by human papilloma virus (HPV). The typical lesions are skin-colored or brown flat papules with 2–5 mm in diameter and mostly appear on the face and extremities in groups with numerous quantities. Flat warts are common in both children and adults. The prevalence can be as high as 20%, in particular, ranging from 4% to 33% in primary school children [1,2]. Warts infections occur by a skin-to-skin contact with infected individuals. Although 66% patients have a spontaneous clearance within two years, many patients do not show involution at all. Most patients with multiple warts in face or hands will need treatments due to cosmetic and social concerns.

Conventional treatments of flat warts include cryotherapy, CO_2 laser, electrosurgery and antimitotic agents (such as podophyllin, bleomycin and retinoids). These treatments have shown various efficacies, but often result in pain, blistering, sore and scar. Choices of treatments will depend on the location, size, number and types of warts. The recurrence is common, especially in patients with multiple warts [3]. Therefore, a combined therapeutic strategy is worthy of investigation to achieve a better outcome on those treatment-resistant flat warts.

Photodynamic therapy (PDT) is a treatment option for many dermatological conditions [4]. With a combination of a photosensitizer that is selectively localized in the target tissue, illumination on the lesion with a visible light will result in a photodamage and subsequent cell death [5]. PDT treatment can damage the virally infected keratinocytes and inactivate viral particles without envelopes. In recent years, many researches have shown that PDT with 5-aminolevulinic acid (5-ALA) can treat recalcitrant facial flats with a good curative effect and low incidence of recurrence [6–8].

The purpose of this study is to retrospectively evaluate the efficacy of 2940-nm ER:YAG laser in combination with PDT as compared with PDT alone on the treatment-resistant flat warts.

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Table 1
Patients' demographics and clinical parameters.

	Age (years)	Gender (F/M)	Duration (months)	Progression /stabilized phase	Pruritus/prickling sensation (Y/N)	Lesion Number
The PDT-only group (n = 40)	27.58 ± 1.09 (14-45)	26/14	33.85 ± 1.24 (22-56)	27/13	18/22	30.95 ± 1.44 (16-55)
The combined group (n = 40)	26.75 ± 1.07 (14-42)	25/15	35.86 ± 1.42 (24-60)	26/14	18/22	31.33 ± 1.33 (18-51)
P	0.592	1	0.600	1	1	0.849

2. Materials and methods

2.1. Patients

Patients with generalized recalcitrant facial flat warts visited our clinics from Jan 2015 to Jan 2017 were selected in this retrospective study. Inclusion criteria include clinical diagnosis of flat warts, with duration of more than 2 years; having received various treatments but ineffective or the flat warts' recurrence; the lesion on face with area > 30%; no optical treatment for two weeks and no systemic therapy for 4 weeks; not scar diathesis.

There were total 80 subjects included in this research. The patients in the PDT-only group (n = 40 patients) received 20% ALA-PDT. The patients in the combined group (n = 40 patients) received an application of 20% ALA-PDT after a 2940-nm ER:YAG laser treatment each time.

2.2. Treatment

For the PDT-only group, the photosensitizer ALA (Fudan-Zhangjiang Biomedicine Co., Ltd., Shanghai, China) was diluted into a final concentration of 20% with 0.9% NaCl, followed by an application to the lesions through swab with three times after skin was disinfected. The ALA solution was allowed to be absorbed by skin, then the lesions were covered with a plastic film to avoid light for 3 h. An irradiation on the whole face with a red light was performed for 3 min, with wavelengths of 633 ± 3 nm and a dosage of 50 mw/cm^2 (Chongqing Derma Photoelectric Technology Co., Ltd., Sichuan, China). In the combined group, the lesions were firstly treated with Profile 2940-nm ER:YAG laser (Sciton, Inc, Palo Alto, CA, USA) single spot abrasion for a depth of 30 μm; followed by 20% ALA-PDT treatment to lesions. All patients received their treatments once per every 2 weeks for 6 weeks and were followed up for 3 months after the final treatment.

2.3. Study evaluation

After each treatment, erythema and edema on the lesions were instantly observed and recorded. Images were taken by a professional photographer at baseline and on week 2, 4, 6 and 12 weeks. The clinical response was evaluated by a blinded investigator through images. 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 response (100%), excellent response (70–100%), good response (30–70%), and poor response (< 30%). The total effective rate in each group was calculated out by dividing the number of patients whose clearance rate was more than 70% with the total number of patients respectively [9,10]. The Visia image system (Canfield Scientific, Inc. USA) was used to quantify the porphyrin fluorescence intensity after PDT [11].

2.4. Statistical analysis

The data was analyzed with SPSS 16.0. A *t*-test and Chi-square test were used for statistical analysis. *P* value < 0.05 was considered significant.

3. Results

3.1. Patients

A total of 80 patients with recalcitrant facial warts were treated with PDT alone (n = 40) or PDT combined with 2940 nm laser (n = 40) in our clinics from Jan 2015 to Jan 2017. The average ages of the PDT-only group and the combined group were 27.58 ± 1.09 and 26.75 ± 1.07 years old, and the disease courses were 33.85 ± 1.24 and 35.86 ± 1.42 months, respectively. The patients in the progression phase were 67.5% (27 patients) and 65% (26 patients) in the PDT-only and combined treatment groups, respectively. Demographics and clinical features of patients were presented in Table 1. The differences between the gender, age, disease duration and the lesion severity of the two groups were not statistically significant.

3.2. Efficacy

After 6 weeks of the first treatment, fourteen out of 40 patients in the combined group were cured, 17 showed excellent responses and 8 showed good responses, with a total effective rate of 77.5% (31/40). In contrast, eight patients in the PDT-only group received PDT alone were cured, 15 showed excellent responses, 11 exhibited good responses, and 6 had poor responses, with a total effective rate of 57.5% (23/40) ($p = 0.0416$). After the first treatment, fifteen (37.5%) patients had good responses in the PDT-only group, and 32(80%) patients in the combined group. After the second treatment, the number of patients with excellent responses were 8 (20%) *vs*. 23 (57.5%), and with good response were 23 (57.5%) *vs*. 15 (37.5%) in the PDT-only group as compared to the combined group, respectively. After the third treatment, complete resolution occurred in 8 patients of the PDT-only group and 14 patients of the combined group (Table 2 and Fig. 1).

The average clearance rates of the lesions in the combined group were significantly higher than the PDT-only groups after each treatment as well as in a total of three treatments (41.03 ± 2.02% *vs*. 25.10 ± 1.56%, $p < 0.0001$; 64.63 ± 2.70% *vs*. 47.00 ± 3.14%, $p < 0.0001$; and 81.68 ± 2.83% *vs* 68.13 ± 3.97%, $p = 0.0068$) (Fig. 2). The combined group showed a faster restoration than the PDT-only group. After three months of follow-up, no relapse occurred in patients from either group.

Table 2
Comparison of treatment efficacies among patients in two groups.

Patient	The PDT-only group			The combined group		
No. (%)	2 weeks	4 weeks	6 weeks	2 weeks	4 weeks	6 weeks
Complete	0	0	8	0	0	14
Excellent	0	8	15	0	23	17
Good	15	23	11	32	15	8
Poor	25	9	6	8	2	0
Total effective rate	23(57.5%)			31(77.5%)※		

Note : ※$p = 0.0416$, $p < 0.05$ in the combined group *vs*. PDT-only group.

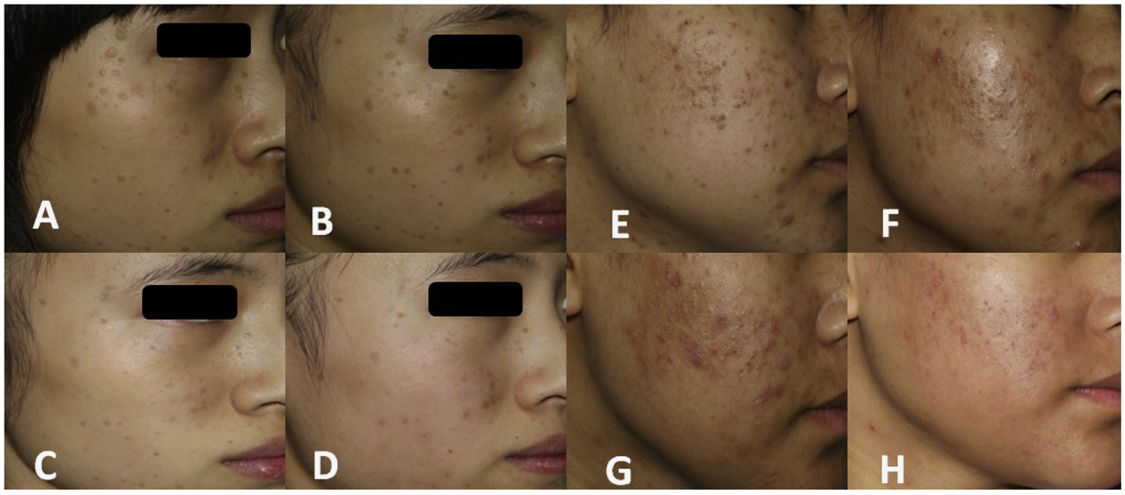

Fig. 1. Improvements on facial warts after PDT treatment alone as compared with PDT + 2940 nm laser. A–D, A 24-year-old female patient, before (A), after the first (B), second (C), and third (D) sessions of PDT treatment alone. E–F, A 21-year-old female patient, before (E), after the first (F), second (G), and third (H) sessions of PDT + 2940 nm laser. The combined group showed a faster restoration than the PDT-only group.

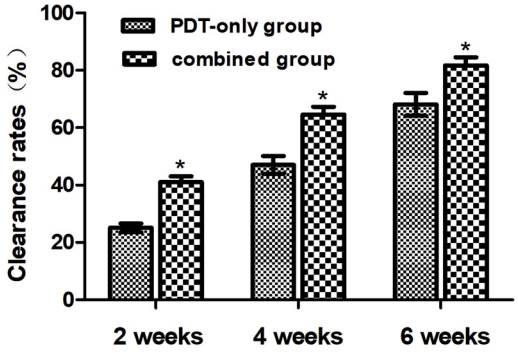

Fig. 2. Clearance rates of lesions in the two groups after multiple times of treatments.
※ $p < 0.05$, the intra-group comparison in the PDT-only *vs.* the combined group.

The ALA can be transformed into fluorescent photosensitizing protoporphyrin IX in the mitochondria upon skin uptake which can be detected by the Visia image system. In the combined group, the skin was immediately assessed after light-impermeable dressing for 3 h, erythema and small scabs were observed. Furthermore, an accumulation of porphyrin in the lesion areas was observed, showing that skin abrasion effectively improved the uptake of ALA (Fig. 3).

3.3. Adverse reactions

The adverse reactions including erythema and mild edema were observed in both groups. The prickling sensation and scratchiness, though tolerable, were more evidently reported by patients in the combined group than in the PDT-only group. Four patients in the combined group showed a manifested mild pigmentation or hypopigmentation; while two patients in the PDT-only group showed a mild pigmentation. All these color changes were restored in three months after the treatment termination. These adverse reactions are speculated to be related to the enhanced absorption of ALA after the skin abrasion.

4. Discussion

Flat warts are mainly caused by HPV types 3, 10, 27 and other subtypes. Pathological manifestations of flat warts include evident hyperkeratosis, hypertrophy of the spinous layer, no papilloma-like hyperplasia, enlarged vacuolated cell in the granular layer and the upper part of the spinous layer, hyperchromasia, and intracellular viral particles [12]. There are multiple therapeutic options for flats warts. The first-line therapies include medical treatments (salicylic acid, silver nitrate, glutaraldehyde) that are useful to treat a single wart or a few and/or small common warts of short duration (less than 1 year). Cryotherapy is the second-line therapy if the above treatments have failed. Third-line therapies including topical, intralesional, systemic, and physical destruction are used for the recurrent or difficult-to-treat

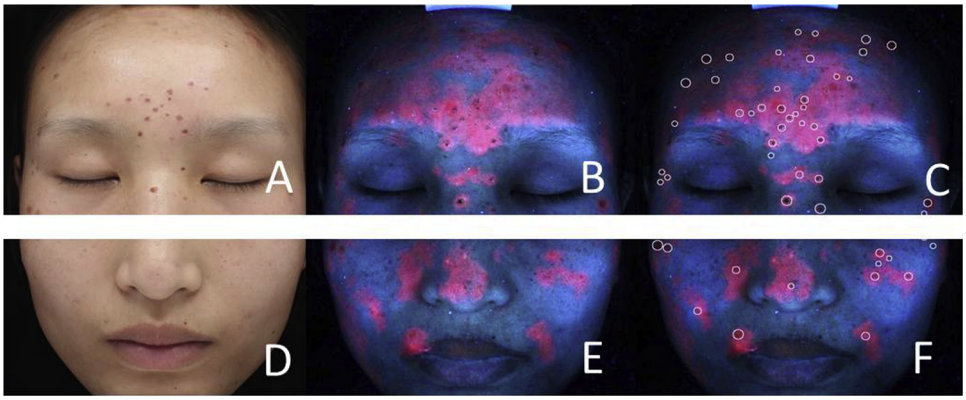

Fig. 3. An accumulation of porphyrin fluorescence after the combined treatment (A–C) or PDT alone (D–F) by the Visia image system. The leisonal warts were marked with white circles (C, F). The 2940 nm laser abrasion facilitated the uptake of ALA in the lesional sites.

lesions [13].

PDT can be achieved by an uptake of topical ALA/MAL in rapid proliferative cells, melanin, blood vessels and sebaceous glands. Upon uptake, the ALA is transformed into protoporphyrin IX (PpIX) in mitochondria and produces singlet oxygen and oxygen free radicals (ROS) to oxidize lipids, amino acid and protein, which will stimulates the release of inflammatory mediators and induction of apoptosis and necrosis, ultimately leading to a destruction of the targeting tissues [14–16]. In recently years, several researches have reported that PDT is an effective treatment for recalcitrant cutaneous warts [17–19]. Yang et al. [20] treated recalcitrant facial flat warts with three sessions of PDT (10% ALA, 3 h, LED 60–100 mW/cm^2), the average effective rate was up to 88.8% at the 24-weeks follow-up, with no recurrences. Qian et al. [17] showed that a step-up therapy of ALA-PDT could also result in excellent effects with low side effects. K. Chen et al. [21] have shown that ALA-PDT can result in a lower recurrent rate as compared to CO_2 laser for the treatment of condylomata acuminate.

PDT shows limited efficacy on many treatment-resistant lesions, in particular those hypertrophied lesions. In order to overcome this clinical barrier, PDT in combination with other treatment options (such as CO_2 lasers) have been attempted to achieve a better outcome [22–25]. For example, KH Yoo et al. [26] reported that MAL-PDT in combination with ablative CO_2 laser showed a good efficacy on the treatment for recalcitrant periungual warts. However, the CO_2 laser-associated side effects such as pain, hyperpigmentation and hypopigmentation have raised concerns to patients and clinicians. Therefore, an alternative wavelength other than CO_2 laser is worthy of investigation for the combination therapies. In this study, we studied whether using a 2940-nm laser in combination with PDT could achieve a better outcome on those treatment-resistant flat warts. The main rationales of choosing 2940-nm laser are as follows. 1) The 2940-nm laser has a very strong water absorption peak. Energy is preferentially absorbed by intracellular water to create rapid heating and vaporization of tissue. It shows no significant residual thermal damage to the surrounding skin and reduced risk of hyperpigmentation as compared to CO_2 laser. 2) The 2940-nm laser can accurately adjust the depth of vaporization, gasification and solidification (4~200 μm), so that the depth of treatment can be more precisely controlled. 3) The faculae of the single spot hand tools have an option of 2 or 4 mm diameter, which can reduce the damage to the surrounding normal skin. 4) The 2940-nm laser may strip the lesion by 30 μm, without reaching the dermis and leaving no scar. 5) The 2940-nm laser can execute a dual function of destruction of wart body structures and facilitation of the uptake of ALA.

In this study, the 2940 nm ER:YAG laser in a combination with PDT was significantly more effective than PDT alone. Our data showed that the 2940-nm ER:YAG laser significantly facilitated the accumulation of ALA on the lesional sites, leading to a better efficacy for subsequent PDT treatment. Currently, the PDT treatment for viral warts has not been standardized due to variables among individuals. Using an image system such as Visia to evaluate the porphyrin fluorescence for a guidance of a PDT dosage will be our future research focus for development of a personalized PDT therapy. In conclusion, 2940-nm ER:YAG laser in a combination with PDT for the treatment of facial numerous flat warts results in significantly better outcomes as compared to PDT alone. It shows a good safety and efficacy profiles with few adverse reactions. This combined therapeutics can be recommended for those flat wart lesions that are ineffective by conventional treatments.

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Conflict of interest

None Declared.

Prior publication

None of the material in this manuscript has been published or is under consideration for publication elsewhere, including internet.

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