

ORIGINAL ARTICLE

Short-term clinical effects of photodynamic therapy with topical 5-aminolevulinic acid for facial acne conglobata: an open, prospective, parallel-arm trial

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Key words:

acne conglobata; Chinese herbal
medicine mask; photodynamic
therapy; red light

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Accepted for publication:

4 July 2013

Conflicts of interest:

None declared.

SUMMARY**Background**

Acne conglobata is hardly curable and easily leads to scar formation after treatment using traditional methods.

Aim

To develop a novel way to treat acne conglobata.

Methods

Seventy-five patients with facial acne conglobata were included in this clinical study and divided into either a treatment group ($n = 35$) to receive photodynamic therapy (PDT) with topical 5% 5-aminolevulinic acid and red light once every 10 days for a month or a control group ($n = 40$) to receive a Chinese herbal medicine mask plus red light once per week for the same duration. Patients in both groups were given oral vitamin capsules, doxycycline, zinc gluconate, and topical metronidazole. Efficacy was evaluated with respect to symptom score, cure rate, and response rate up to 2 weeks following the final treatment, and time points for assessment included baseline (D_0), the visit before each treatment (D_{10} and D_{20} for the treatment group, and D_7 , D_{14} , and D_{21} for the control group), and 2 weeks after treatment (D_{34} for the treatment group and D_{35} for the control group). Safety was assessed by recording adverse effects.

Results

Treatment with PDT significantly improved acne lesions and reduced scar formation. The treatment group had a significantly lower symptom score, a higher cure rate, and response rate than the control group. No systemic side effects occurred.

Conclusion

The treatment of acne conglobata with PDT is associated with a high cure rate, short treatment period, few side effects, and reduced scar formation. To the best of our knowledge, this is the first report on the treatment of acne conglobata with PDT.

Photodermatol Photoimmunol Photomed 2013; 29: 233–238

Acne is a common chronic inflammatory disorder characterized by the presence of blackheads, pustules, and potentially cysts and scars on the face, back, and chest, affecting an estimated 80% of adolescents and persisting in approximately 3% of middle-aged adults (1). Cystic acne is the most severe type of acne that affects deep skin tissue and can cause swelling, bleeding, pain, scarring, or changes in skin pigmentation. These blemishes can lead to low self-esteem, restriction of daily activity, and even clinical depression (2). Currently, there are many treatments available for acne, including topical or oral antibiotics, topical retinoids, and oral isotretinoin (3). While acne vulgaris is easily managed, the clinical effects of conventional treatments for cystic acne are often unsatisfactory because of an extended course of therapy, development of drug resistance, side effects, recurrence, and failure to prevent scar formation (2). Therefore, there is a need to develop alternative treatments for cystic acne.

Photodynamic therapy (PDT) is a form of phototherapy that involves the activation of a nontoxic light-sensitive compound by irradiation with light to cause selective cytotoxic destruction. In recent years, PDT has been increasingly used for a wide variety of neoplastic, inflammatory, and infectious dermatologic conditions, such as psoriasis, cutaneous T-cell lymphoma, and warts (4). Previous clinical studies have assessed the efficacy, safety, and cosmetic outcome of PDT in the management of acne and found that PDT could provide favorable results with tolerable side effects (5–9), suggesting that PDT is an effective and safe treatment option for acne (10). However, the majority of studies so far reported focused on mild to moderate acne, and there have been few clinical reports on the effects of PDT on severe forms of acne, such as cystic acne (11, 12).

Acne conglobata, marked by suppuration, cysts, sinuses, and scarring, is a severe form of cystic acne that is most difficult to manage (2). Although various therapeutic modalities for acne conglobata have been explored (13, 14), the therapeutic effects are unsatisfactory. Currently, there have been no studies examining whether PDT is effective and safe in the management of acne conglobata. The aim of the present study was to evaluate the efficacy and safety of PDT with topical 5-aminolevulinic acid (ALA), the most commonly used PDT agent that has been approved by the US Food and Drug Administration for the treatment of actinic keratosis (4), in the management of acne conglobata by comparing with Chinese herbal medicine mask plus red light. The Chinese herbal medicine mask is our self-developed acne care regimen that can exert anti-inflammatory actions. Over 3 years of clinical use has supported that

this regimen is effective and safe in the management of acne (our unpublished observation).

PATIENTS AND METHODS

Patients

This was an open, prospective, parallel-arm clinical study. The study protocol was approved by the Ethics Committee of Lanzhou General Hospital of Lanzhou Military Area Command (Lanzhou, China). Seventy-five patients with facial acne conglobata, who were treated at the Department of Dermatology of Lanzhou General Hospital of Lanzhou Military Area Command (Lanzhou, China) from May 2011 to September 2012, were included in the study. Inclusion criteria included the presence of lesions involving the whole face, number of cystic lesions larger than 1 cm in diameter ≥ 6 , poor response to medication therapy, and being willing to participate in the study and sign the informed consent form. Patients were excluded if they had a history of photosensitivity or allergy to drugs or food, were pregnant, lactating, or menstruating. The included patients were divided into a treatment group ($n = 35$) and a control group ($n = 40$) based on the patient's personal finance and interests. The treatment group underwent PDT, while the control group was treated with Chinese herbal medicine mask plus red light. Both treatments were performed on an outpatient basis. Each patient signed the informed consent form and was photographed before each treatment.

Treatments

ALA-PDT was performed using red light. Before application of ALA, the skin was cleansed, and a freshly prepared 5% ALA solution (Fudan-Zhangjiang Bio-Pharmaceutical, Shanghai, China) was applied to the lesions for 3 h under occlusion; the lesions were illuminated with red light (633 ± 10 nm, 100 mW/cm², 50 J/cm²) for 20 min using a light irradiation apparatus with a LED-IB lamp (Yage Optic and Electronic Technique, Wuhan, China). The treatment was given once every 10 days for a month (a total of three treatments). The total cost for ALA-PDT per cycle was 4035 yen (RMB).

For treatment with Chinese herbal medicine mask plus red light, the skin was cleansed and disinfected with chlorhexidine acetate. Following acne extrusion with an acne needle, Chinese herbal medicine mask (consisting mainly of honeysuckle, forsythia, Chinese violet, selfheal, purslane, stiff silkworm, cypress, and white thistles) was applied for 20 min. The lesions were then illuminated with

red light for 20 min (633 ± 10 nm, 100 mW/cm², 90 J/cm²) using the same light source as ALA-PDT. The treatment was given once every week for a month (a total of four treatments). The total cost for the Chinese herbal medicine mask regimen per cycle was 816 yen (RMB).

Patient in both groups were given oral vitamin capsules 25 mg tid, doxycycline 0.1 g bid, zinc gluconate 70 mg tid, and topical metronidazole gel bid, simultaneously with the PDT or Chinese herbal medicine mask plus red light. After the primary treatment, patients who were showing signs of recovery were given these medications for 1 more month to reinforce treatment effects, while those who did not respond to or were intolerant of the treatment were given other treatments.

Efficacy evaluation

Patients who underwent two or more treatments were considered eligible for efficacy evaluation. At baseline (D₀), the visit before each treatment (D₁₀ and D₂₀ for the treatment group, and D₇, D₁₄, and D₂₁ for the control group), and 2 weeks after treatment (D₃₄ for the treatment group and D₃₅ for the control group), the numbers of acne lesions (including comedones, papules, pustules, nodules, and cysts) were counted to calculate symptom score (SS) at each time point. Acne lesions were scored as follows: 0.1 point for the presence of each comedone, 0.2 point for each papule, 0.3 point for each pustule, 0.5 point for each nodule, 1 point for each cyst smaller than 1 cm in diameter, 2 points for each cyst greater than 1 cm in diameter, and 3 points for each conglobate cyst. SS for a patient was the sum of the scores for all counted lesions. SS reduction index (SSRI) was then calculated as $[\text{Scores (pretreatment SS)} - \text{Scores (posttreatment SS)}] / \text{Scores (pretreatment SS)} \times 100\%$. Treatment efficacy was divided into four levels based on the SSRI: cure (SSRI $\geq 90\%$), significant improvement ($60\% \leq \text{SSRI} < 90\%$), improvement ($20\% \leq \text{SSRI} < 60\%$), and ineffective (SSRI $< 20\%$). Effective rate was defined as the proportion of improved patients. Response rate was defined as the proportion of cured and improved patients. Cure rate, effective rate, and response rate were calculated based on the SSRI at baseline (D₀) and 2 weeks after treatment (D₃₄ and D₃₅).

Safety evaluation

All patients were evaluated for safety. Adverse effects were recorded throughout the study, including erythema, swelling, scaling, pustules, blisters, pruritus, pain, and pigmentation. The time for appearance and remission, severity, treatments, and outcome of adverse events were recorded.

Routine blood and urine tests and assays of liver and renal function and electrolytes were performed before treatment and after the last treatment.

Statistical analysis

Statistical analyses were performed using SPSS 13.0 software (SPSS Inc., Chicago IL, USA). Numerical data are expressed as mean \pm standard deviation. Pretreatment and posttreatment SS was compared using the paired *t*-test. Cure rate and response rate between the two groups were compared using the chi-squared test. *P*-values < 0.05 were considered statistically significant.

RESULTS

Follow-up information and demographic characteristics

A total of 75 patients with acne conglobata, including 35 in the treatment group and 40 in the control group, were originally enrolled in the study. Three (9.38%) patients in the treatment group discontinued therapy because of dissatisfaction with therapeutic effect (one case), too high cost (one case), or switch to oral Chinese medicine (one case). Five (14.29%) patients in the control group were lost to follow-up because of dissatisfaction with therapeutic effect (two cases), having no time (one case), switch to oral Chinese medicine (one case), or failure to contact (one case). As a result, data analysis was performed on 32 subjects (21 males and 11 females) in the treatment group and on 35 subjects (21 males and 14 females, including one lost to follow-up after two treatments) in the control group. Patients of the two groups had comparable gender composition, age (22.32 ± 1.05 years vs. 21.27 ± 1.57 years, $P > 0.05$), disease history (2.25 ± 0.76 months vs. 2.32 ± 0.56 months, $P > 0.05$), and severity of acne lesions (SS: 32.51 ± 6.23 vs. 29.87 ± 3.96 months, $P > 0.05$).

Efficacy

Prior to treatment, the patients had a large number of pustules, nodules, and cysts on their face, and some cysts fused together to form larger cysts (Fig. 1a–c). Ten days after the first PDT, the number and severity of the lesions were significantly reduced in the majority of patients (Fig. 1d–f). After the second PDT, the lesions were further improved (Fig. 1g–i). Compared with pretreatment values, SS was significantly reduced in both the treatment group (32.51 ± 6.23 vs. 5.32 ± 0.19 , $P < 0.001$) and control group (29.87 ± 3.96 vs. 10.46 ± 1.11 , $P < 0.01$) after treatment.



Fig. 1. A typical case of facial acne conglobata. (a–c) Condition of the patient before photodynamic therapy (PDT). (d–f) Ten days after the first PDT. (g–i) Twenty-one days after the second PDT. The treatment response in this patient was rated as ‘cured’, and improvement was less remarkable in other treated patients.

Although pigmentation developed in some severe cases, no scars formed. The treatment group had significantly lower SS (5.32 ± 0.19 vs. 10.46 ± 1.11 , $P < 0.01$) and higher cure rate (87.50% vs. 62.86%, $P < 0.01$) and response rate (100% vs. 91.43%, $P < 0.05$) than the control group (Table 1).

Safety

In the treatment group, seven (21.88%) patients developed mild to moderate erythematous swelling and pain after the first treatment, which could be relieved by ice application and did not affect subsequent treatments. Five (15.63%) patients developed significant erythematous swelling, increased number of cysts, and severe pain and had to receive other treatments. In the control group, six (17.14%) patients developed mild erythema and pain after

the first treatment, which could be relieved by ice application and did not affect subsequent treatments. No abnormalities were observed in routine blood and urine tests and assays of liver and renal function and electrolytes. No systemic adverse reactions occurred.

DISCUSSION

Previous studies have indicated that PDT has good clinical efficacy in the management of mild to moderate acne with tolerable side effects (5–9). In the present study, we compared the efficacy and safety of PDT with topical 5-ALA vs. Chinese herbal medicine mask plus red light in the treatment of acne conglobata. We found that, although the total cost for the Chinese medicine regimen was relatively low, PDT with topical 5-ALA could clear pustules, nodules, and cysts and prevent scar formation, and was

Table 1. Efficacy in the two treatment groups

Group	Number of patient	Symptom score		Cure rate (%)	Effective rate (%)	Response rate (%)
		Pretreatment	Posttreatment			
Treatment	32	32.51 ± 6.23	5.32 ± 0.19*,***	28 (87.50)*	4 (12.50)	32 (100)****
Control	35	29.87 ± 3.96	10.46 ± 1.11**	22 (62.86)	10 (28.57)	32 (91.43)

* $P < 0.001$.** $P < 0.01$ vs. pretreatment.*** $P < 0.01$.**** $P < 0.05$ vs. the control group.

associated with a higher cure rate and response rate and mild adverse effects. These data suggest that PDT with topical 5-ALA is a promising potential treatment for acne conglobata.

Acne conglobata is an uncommon and unusually severe acne variant that often produces pronounced disfigurement and is much more difficult to treat compared with cystic acne (2). Although the etiology and pathogenesis of this severe type of acne remain unknown, it may be associated with testosterone, changes in reaction to *Propionibacterium acnes* bacteria, use of anabolic steroids, androgen-producing tumors, and even hereditary factors (15, 16). Because acne conglobata can cause disfiguring scars if not treated, it must be aggressively managed. The treatments for acne conglobata includes oral isotretinoin, alone or in combination with systemic steroids (17), oral antibiotics, dapsone (18), infliximab (19), carbon dioxide laser (20), external beam radiation (21), and targeted therapies (22). Although some success can be achieved using these strategies, the results are not very satisfactory because of treatment resistance, scar formation, and severe adverse effects. Our finding that PDT with topical 5-ALA could prevent scar formation in the majority of patients with acne conglobata suggests that PDT is a viable alternative to conventional treatments for this severe form of acne.

Previous studies have demonstrated that PDT, which is suitable for patients of all ages and lifestyles, is a safe and effective therapeutic modality for various dermatologic conditions (23). The specific mechanisms of action involved in PDT with topical 5-ALA for acne includes induction of phototoxic injury of sebaceous glands, inhibition of sebum production, photodynamic killing of *Propionibacterium acnes*, and alleviation of follicular obstruction (3). Compared with other forms of facial therapies, PDT has diverse advantages. For example, this technique allows for rapid treatment of acne lesions all over the face and has minimal recovery time. Furthermore,

PDT is less destructive and painful than many of the deep peels and lasers. In addition, PDT is not associated with surgical excisions or systemic side effects. More importantly, PDT causes no scarring, as demonstrated in the present study.

Despite many advantages, the PDT technique has several disadvantages. Firstly, this technique is associated with adverse effects, such as erythema, skin peeling, pain, burning, stinging, exfoliation, and post-inflammatory hyperpigmentation (3, 24). In the present study, erythematous swelling, increased number of cysts, pigmentation, and severe pain were observed in few patients treated by PDT. As PDT was used for the management of acne for a limited time frame, its long-term side effects are unknown. Furthermore, 5-ALA requires time to convert into protoporphyrin IX and penetrate into the skin, and topical ALA has to be applied for a relatively long period under occlusion (3). In addition, strict photoprotection is needed after the treatment procedure to avoid phototoxicity (25). The use of new photosensitizers may help overcome these problems (3).

Of note, quite a high cure rate is evident in the control group; however, this was not unexpected because the patients of this group received a combination of cleansing and disinfection with chlorhexidine acetate, Chinese herbal medicine mask, red light, and drug treatment. On one hand, the Chinese herbal medicine mask appears to have good anti-inflammatory actions (our unpublished observation). On the other hand, the combination of several mild treatments might cause better results than each monotherapy.

This study has several limitations. First, the nonrandom assignment of subjects to treatment and nonblind design are major limitations of the present study. Second, the treatment parameters, including pretreatments, posttreatments, ALA contact time, light sources, and numbers of sessions associated with PDT, were not optimized. As a

consequence, therapeutic results might not be definitive. Finally, the lack of long-term follow-up data because of the relatively short follow-up period was another drawback of the study. Future long-term, blinded, randomized studies are required to address these issues.

In conclusion, in the present study, we demonstrate that PDT is superior to Chinese herbal medicine mask plus red

light in the treatment of acne conglobata, which is hardly curable and easily lead to scar formation after treatment using traditional methods, in terms of cure rate, response rate, and reduced scar formation, representing an effective therapeutic option for patients who do not respond to other therapeutic modalities or are unwilling to take long-term medication.

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