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ORIGINAL RESEARCH

Retrospective Study of Factors Affecting Efficacy of Therapy with Dye Pulsed Light for Erythematotelangiectatic Rosacea

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ABSTRACT

Introduction: Dye pulsed light (DPL) was proven to be effective at treating erythematous and telangiectatic skin disorders. However, there are limited data on the efficacy of DPL treatment for erythematotelangiectatic rosacea (ETR), and researchers do not fully understand the factors that may affect the efficacy. Here, we performed a study to investigate the efficacy of DPL treatment for ETR and determine the factors affecting that efficacy.

Methods: Sixty-five patients with ETR underwent three treatment sessions with DPL at 4-week intervals and were followed up at 4 weeks after the last treatment session. Skin type, sex, age, lesion site, severity of erythema and telangiectasia, VISIA percentile ranking, clinical photographs and red area images were recorded at baseline. The post-treatment erythematous and telangiectatic scores and VISIA percentile rankings were recorded, and the effects of different personal and clinical factors on the efficacy were statistically analysed.

Results: The erythema and telangiectasia scores and VISIA percentile rankings showed significant improvement after the DPL procedures ($p < 0.01$). With regard to erythema, treatment efficacy was not affected by any of the investigated variables, including pre-treatment erythema scores, skin type, pre-treatment VISIA percentile ranking, sex, age and lesion site ($p > 0.05$). With regard to telangiectasia, the treatment efficacy was greater for mild telangiectasia than for severe telangiectasia (odds ratio = 4.14, $p < 0.05$). There was no significant difference in treatment efficacy between the moderate and severe categories (odds ratio = 4.00, $p > 0.05$).

Conclusion: DPL is not the optimal procedure for treating severe telangiectasia in patients with ETR, whereas the efficacy of the treatment for erythema was not affected by the severity of the condition.

Keywords: Dye pulsed light; Efficacy; Erythema; Erythematotelangiectatic rosacea; Telangiectasia

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Key Summary Points

Why carry out this study?

Dye pulsed light (DPL) was indicated to be effective and safe at treating facial telangiectasia; however, there are limited data on the efficacy of the treatment of erythematotelangiectatic rosacea (ETR) with DPL

This study investigated the erythematous and telangiectatic treatment efficacy and whether personal and clinical factors affected the efficacy of treatment

What was learned from the study?

The erythema and telangiectasia scores and VISIA percentile rankings of patients with ETR showed significant improvement after the DPL procedures

The efficacy of the treatment of erythema was not affected by lesion severity, whereas the treatment of severe telangiectasia was not as effective as the treatment of mild telangiectasia

DPL is not suitable for the treatment of ETR with severe telangiectasia

INTRODUCTION

Rosacea is a common chronic cutaneous disorder with features of flushing, erythema, papulopustules, telangiectasia and rhinophyma. Erythematotelangiectatic rosacea (ETR) is one subtype of rosacea. It is characterized by flushing and persistent central facial erythema, and telangiectasis is common [1]. Various types of lights and lasers have been used for the treatment of rosacea [2, 3]. Among these procedures, intense pulsed light (IPL) is safe and effective for the treatment of vascular forms of rosacea. Liu et al. reported that IPL with a wavelength from 540 to 950 nm is a safe and effective treatment for rosacea-associated erythema [4]. Dye pulsed light (DPL) covers a narrow spectrum of wavelengths of pulsed light from 500 to 600 nm. It is also called narrow-band intense pulsed light. Compared with IPL, it targets haemoglobin more specifically, with a higher degree of absorption [5]. DPL was also proved to be effective and safe for the treatment of facial telangiectasia [6].

However, there have been limited reports on the efficacy of DPL for the treatment of erythematous and telangiectatic lesions, and little is known about whether personal and clinical factors can impact the efficacy of therapy with DPL in patients with ETR. In this study, we evaluated the therapeutic efficacy of DPL for both erythematous and telangiectatic lesions using subjective grading scales and objective VISIA percentile rankings. Additionally, the personal and clinical factors affecting the therapeutic efficacy were determined.

METHODS

Patients

A total of 65 patients with ETR who visited the Dermatology Department of the General Hospital of Tianjin Medical University and were treated with DPL between June 2018 and February 2020 were retrospectively evaluated. Before undergoing the procedures, all patients provided written informed consent for their photographs and data to be published in the article. The study adhered to the principles in the World Medical Association's Declaration of Helsinki, and ethics approval for this study was granted by the Ethics Committee of Tianjin Medical University General Hospital (No. IRB2020-WZ-093). We applied the term "persistent centrofacial erythema associated with periodic intensification by potential trigger factors" as a diagnostic criteria for rosacea. Meanwhile, two major features of rosacea including the flushing/transient erythema and centrofacial distribution of telangiectasia were considered as necessary for the inclusion criteria of rosacea patients with ETR subtype in our research [1, 7]. Personal and clinical factors were recorded, including sex, age, lesion sites, skin

type, erythematous and telangiectatic lesion severity, and VISIA percentile rankings. We adopted the Clinician Erythema Assessment (CEA) scale to grade the erythema [7]. The telangiectasia grading scale is as follows: 0 = none, 1 = mild (fine vessels less than 0.2 mm in diameter covering less than 10% of the face), 2 = moderate (several fine vessels and/or a few large vessels greater than 0.2 mm in diameter covering 10–30% of the face) and 3 = severe (many fine and/or large vessels greater than 0.2 mm in diameter covering more than 30% of the face) [8]. Prior to each treatment and at the follow-up visits, clinical photographs and images of the red areas of the rosacea lesions were captured by the VISIA 6.0 Complexion Analysis System (Canfield Scientific Inc, Fairfield, NJ, USA).

Treatment Regimens

The patients were treated with DPL (Harmony XL, Alma Lasers Ltd. Caesarea, Israel) at a wavelength range from 500 to 600 nm with a pulse duration of 10–15 ms and a fluence of 8.4–10.6 J/cm^2. The spot size was 1 cm × 3 cm, with an overlap area of 15–20% during the treatment. Cold water spray and an icepack were applied during and after the procedure, respectively. Immediate darkening or fading of the treated erythema and blurring, disappearance or blanching of the dilated blood vessels were considered clinical indicators of the treatment endpoints. A total of three sessions at 4-week intervals were delivered.

Follow-Up and Efficacy Evaluation

All patients were followed up at 12 weeks after the baseline evaluation (Fig. 1). Three blinded independent dermatologists reviewed the clinical photographs before and after DPL therapy to determine the erythema and telangiectasia grades. VISIA red area evaluations were performed at weeks 0 and 12. The VISIA score was presented with the percentile ranking, and a higher score indicated a better skin condition. If the post-treatment scores for erythema or telangiectasia were higher than or equal to the pre-treatment scores, the efficacy was defined as "not responsive"; if the post-treatment scores for erythema or telangiectasia were lower than the pre-treatment ones, the efficacy was defined as "responsive".

Statistical Analysis

SPSS v. 23.0 (IBM Corp, Armonk, NY, USA) was used for the statistical analysis. Wilcoxon signed-rank tests were used to compare the pre-treatment and post-treatment erythema and telangiectasia scores and VISIA percentile rankings. Chi-square tests and Fisher's exact tests were used to analyse differences in categorical data between the "responsive" and "not responsive" groups, and significant univariable

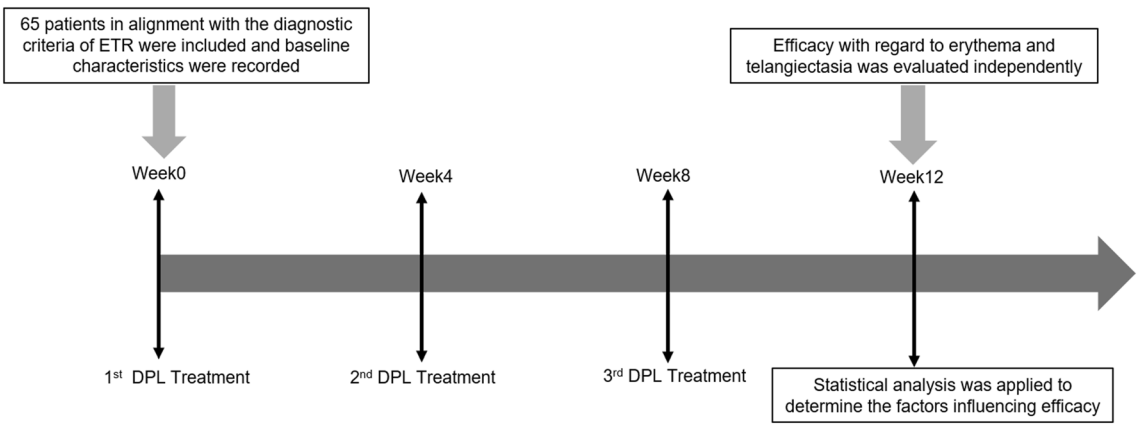

Fig. 1 Study flow chart of materials and methods. ETR erythematotelangiectatic rosacea, DPL dye pulsed light

results were examined in multivariate logistic regression. The VISIA percentile rankings are presented as interquartile ranges (IQRs). Mann–Whitney *U* tests were performed to analyse the difference in VISIA percentile rankings between the "responsive" and "not responsive" groups. Statistical significance was defined as a *p* value less than 0.05. GraphPad Prism 8.0 (GraphPad Software, La Jolla, CA, USA) was used to graph the data.

Table 1 Baseline characteristics of patients with ETR

Characteristics	Cases, *N* (%)/IQR
Pre-treatment T scores	
1	26 (40.00)
2	16 (24.62)
3	23 (35.39)
Pre-treatment VPR	(1.00, 10.00)
Skin types	
Fitzpatrick II	21 (32.31)
Fitzpatrick III	28 (43.08)
Fitzpatrick IV	16 (24.62)
Pretreatment E scores	
1	10 (15.38)
2	34 (52.31)
3	8 (12.31)
4	13 (20.00)
Sex	
Male	20 (30.77)
Female	45 (69.23)
Age	
$\leq$ 40 years old	51 (78.46)
$>$ 40 years old	14 (21.54)
Lesion sites	
Nasal alone	16 (24.62)
Nasal and extra-nasal	16 (24.62)
Extra-nasal alone	33 (50.77)

ETR erythematotelangiectatic rosacea, *T* telangiectasia, *E* erythema, *VPR* VISIA percentile rankings, *IQR* interquartile range

RESULTS

The baseline characteristics of the patients with ETR are presented in Table 1. Clinical photographs and red area images (VISIA) of patients with ETR with different severities of erythema and telangiectasia in different treatment efficacy groups are presented in Fig. 2 (front view). The post-treatment scores for erythema and telangiectasia and VISIA percentile rankings showed significant improvement after three DPL treatment sessions ($p < 0.01$, shown in Fig. 3). For erythema and telangiectasia, there were 10 (15.38%) and 31 (47.69%) patients, respectively, who were not responsive to treatment with DPL. With regard to the treatment of erythema, there were no significant differences of pre-treatment erythema score, skin type, pre-treatment VISIA percentile ranking, sex, age and lesion sites between the "responsive" and "not responsive" groups ($p > 0.05$, Table 2). With regard to the treatment of telangiectasia, the univariate statistical analysis of the factors affecting the efficacy revealed that pre-treatment VISIA percentile rankings, sex, age and lesion sites were not significantly different between "responsive" and "not responsive" groups ($p > 0.05$, Table 3). The pre-treatment telangiectasia score and skin type were significantly different between the "responsive" and "not responsive" groups ($p < 0.05$, Table 3). To further analyse the factors affecting the efficacy of DPL for the treatment of ETR, the pre-treatment telangiectasia score and skin type were regarded as independent variables in multivariate logistic regression. When Fitzpatrick skin type IV was taken as the reference, the results showed that the skin type did not significantly affect the treatment efficacy (Fitzpatrick skin type III: odds ratio = 2.67 [95% CI 0.63, 11.42], $p = 0.18$; Fitzpatrick skin type II: odds ratio = 3.19 [95% CI 0.60, 17.02], $p = 0.17$; Table 3). When the severe category of pre-treatment telangiectasia was taken as the reference, the efficacy of treatment in patients in the mild

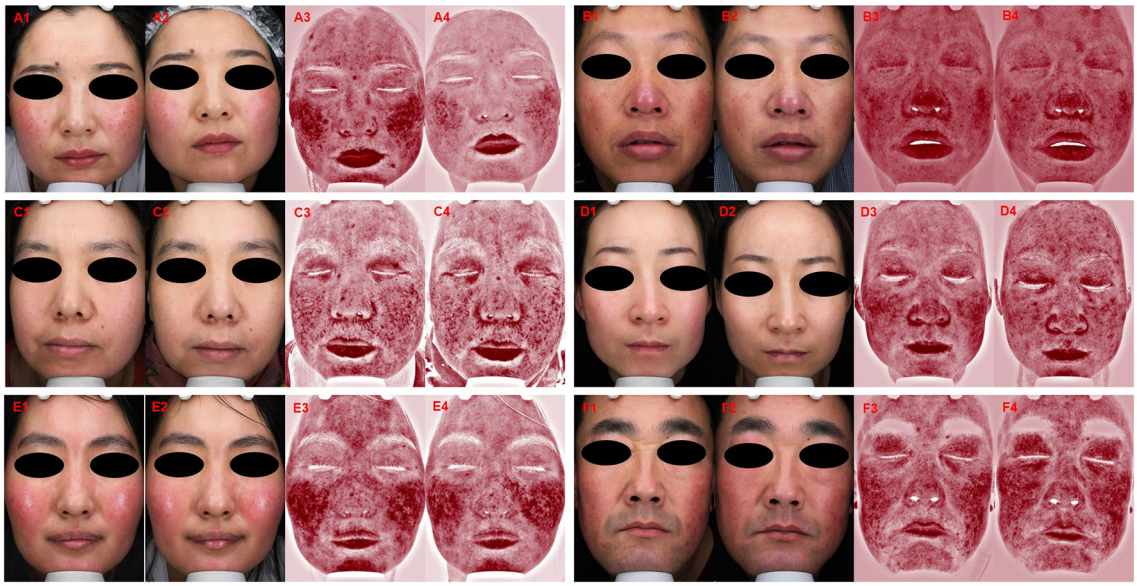

Fig. 2 Clinical photographs and red area images (VISIA) of patients with ETR with different severities of erythema and telangiectasia in different efficacy groups (front view). A–D patients with ETR with erythema severity scores of 2, 2, 1 and 1 and telangiectasia severity scores of 3, 2, 1 and 2 in the responsive group; A1–D1 pre-treatment clinical photographs; A2–D2 post-treatment clinical photographs; A3–D3 pre-treatment red area images (VISIA); A4–D4 post-treatment red area images (VISIA); E patient with ETR with erythematous severity score of 3 and telangiectatic severity score of 3 with erythematous treatment response and without telangiectatic treatment response; F patient with ETR with erythema severity score of 3 and telangiectasia severity score of 2 without treatment response; E1–F1 pre-treatment clinical photographs; E2–F2 post-treatment clinical photographs; E3–F3 pre-treatment red area images (VISIA); E4–F4 post-treatment red area images (VISIA). ETR erythematotelangiectatic rosacea

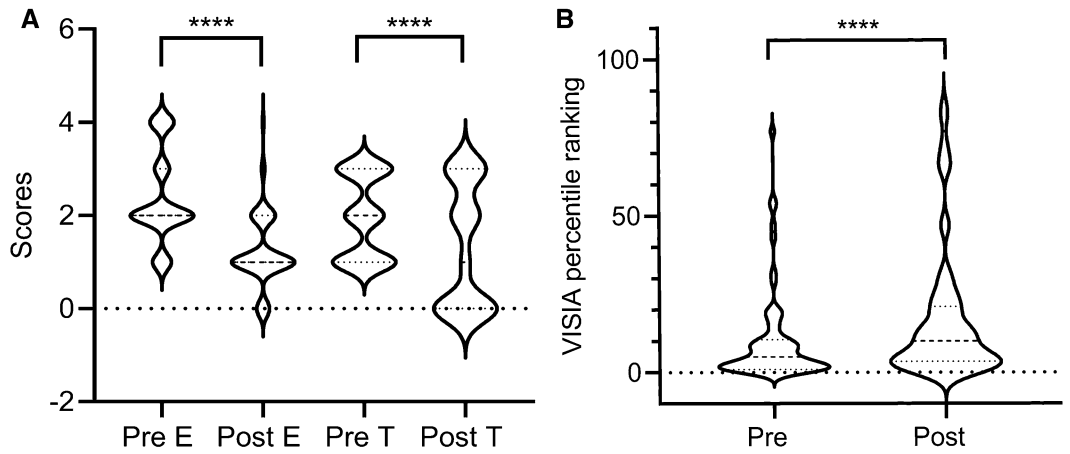

Fig. 3 Changes in baseline erythema and telangiectasia scores (**a**) and VISIA percentile rankings (**b**) at 4 weeks after the last treatment session. There were statistically significant differences between baseline and post-treatment erythematous and telangiectatic scores and VISIA percentile rankings. (****$p < 0.01$) Pre pre-treatment, E erythema, Post post-treatment, T telangiectasia

Table 2 Univariate analysis of personal and clinical factors of patients with ETR in different erythematous treatment efficacy groups

Variables	Responsive cases, *n* %)/IQR	Not responsive cases, *n* (%)/IQR	χ^2/U	*p*
Pre-treatment E scores				
1	8 (12.31)	2 (3.08)	3.36	0.31
2	27 (41.54)	7 (10.77)		
3	7 (10.77)	1 (1.54)		
4	13 (20.00)	0 (0.00)		
Skin types				
Fitzpatrick II	18 (27.69)	3 (4.62)	0.30	1.00
Fitzpatrick III	23 (35.38)	5 (7.69)		
Fitzpatrick IV	14 (21.54)	2 (3.08)		
Pre-treatment VPR	(1.00, 10.00)	(7.00, 29.00)	171.50	0.06
Sex				
Male	15 (23.08)	5 (7.69)	1.12	0.29
Female	40 (61.54)	5 (7.69)		
Age				
$\leq$ 40 years old	44 (67.69)	7 (10.77)	0.08	0.77
$>$ 40 years old	11 (16.92)	3 (4.62)		
Lesion sites				
Nasal alone	12 (18.46)	4 (6.15)	2.48	0.28
Nasal and extra-nasal	13 (20.00)	3 (4.62)		
Extra-nasal alone	30 (46.15)	3 (4.62)		

ETR erythematotelangiectatic rosacea, *E* erythema, *VPR* VISIA percentile rankings, *IQR* interquartile range

telangiectatic category was significantly better than that in patients in the severe category (odds ratio = 4.14 [95% CI 1.15, 14.94], $p = 0.03$; Table 3), although there was no significant difference in the efficacy between the patients in the moderate and severe categories (odds ratio = 4.00 [95% CI 0.79, 20.25], $p = 0.10$; Table 3).

DISCUSSION

Rosacea is a typical cutaneous disease that can cause not only physical but also emotional distress due to many severe symptoms [9, 10]. For ETR, which presents with erythema and telangiectasia as the primary symptoms, laser treatments have been proven to be effective [11, 12]. In recent years, the successful treatment of ETR with IPL has been widely documented [13–16]. Traditional IPL is safe for the treatment of telangiectasia with minimal downtime, low cost and mild adverse reactions. However, the wide range of wavelengths (500–1200 nm) results in less absorption of the energy by haemoglobin, and the clinical efficacy needs to be improved [17]. DPL is a novel type of IPL, and the relatively high absorption

Table 3 Univariate and multivariate analysis of personal and clinical factors of patients with ETR in different telangiectatic treatment efficacy groups

Variables	Responsive cases, *n* (%)/IQR	Not responsive cases, *n* (%)/IQR	χ^2/U	*p*	Adjusted OR (95% CI)	Adjusted *p**
Pre-treatment T scores						
1	17 (26.15)	9 (13.85)	9.86	0.01	4.14 (1.15, 14.94)	0.03
2	11 (16.92)	5 (7.69)			4.00 (0.79, 20.25)	0.10
3	6 (9.23)	17 (26.15)			Reference	
Skin types						
Fitzpatrick II	14 (21.54)	7 (10.77)	6.78	0.03	3.19 (0.60,17.02)	0.17
Fitzpatrick III	16 (24.62)	12 (18.46)			2.67 (0.63, 11.42)	0.18
Fitzpatrick IV	4 (6.15)	12 (18.46)			Reference	
Pre-treatment VPR	(1.00, 10.00)	(2.00, 15.00)	447.00	0.29		
Sex						
Male	9 (13.85)	11 (16.92)	0.62	0.43		
Female	25 (38.46)	20 (30.77)				
Age						
$\leq$ 40 years old	29 (44.62)	22 (33.85)	1.97	0.16		
$>$ 40 years old	5 (7.69)	9 (13.85)				
Lesion sites						
Nasal alone	11 (16.92)	5 (7.69)	2.39	0.30		
Nasal and extra-nasal	8 (12.31)	8 (12.31)				
Extra-nasal alone	15 (23.08)	18 (27.69)				

ETR erythematotelangiectatic rosacea, *T* telangiectasia, *VPR* VISIA percentile rankings, *IQR* interquartile range, *OR* odds ratio

*The adjusted OR and *p*: the model incorporated the factors including the pre-treatment T score and skin type into the multivariate logistic model as confounders

by deoxyhaemoglobin and oxyhaemoglobin eventually leads to higher efficacy rate than IPL in treating the erythematotelangiectatic skin diseases [18].

In our study, during the follow-up period, the scores for erythema and telangiectasia were significantly lower than those at baseline ($p < 0.01$), and the VISIA percentile rankings were higher than those at baseline ($p < 0.01$). The results showed that DPL could improve skin condition in patients with ETR. We found that 84.62% of patients with erythema achieved clinical improvements according to CEA, while only 52.31% of the patients with telangiectasia achieved clinical improvements. The percentages of patients achieving a treatment response

in our study were similar to those in previous studies [18, 19]. However, they were lower than those reported by Gan et al. and Tsunoda et al. [6, 20]. The reason for the lower treatment response rates in our study may be that we performed only three treatment sessions rather than the five sessions applied by Gan et al. Tsunoda et al. employed a two-step irradiation with IPL; the second irradiation was performed with a small spot size (6.35 mm diameter) [20]. In our study, we used a DPL with a spot size of 1 cm × 3 cm, which was larger than that applied in the research performed by Tsunoda et al. A smaller spot size in IPL treatment allows the use of high-fluence irradiation for large capillary dilation, resulting in better efficacy. The efficacy of using a smaller spot size and more treatment sessions for patients with ETR is worth investigating in a future study.

Lim et al. found that there were significant differences in efficacy between the mild group and the moderate/severe group [16]. However, they did not rate the severity of erythema and telangiectasis independently; the major features of telangiectasia did not include the size of the vessels and the extent of involvement, as recommended by the global ROSacea COnsensus (ROSCO) panel [7]. Furthermore, they did not perform multivariate statistical analysis to exclude confounding by variables such as skin type, lesion anatomical site and sex. In our study, we found that there was a significant difference in the efficacy between the mild and severe groups but not between the mild and moderate groups for telangiectasia ($p < 0.05$). As a result of the limited penetration of DPL, it cannot reach the depth necessary to eventually cause thermal coagulation and the closure of vessels. We can conclude that after sufficient DPL treatment, the efficacy with regard to the treatment of erythema in patients with ETR is satisfying regardless of the severity of erythema, while for severe types of telangiectasia in patients with ETR, alternative light or laser therapy can be considered [21–23]. In addition, a combination of light or laser sources rather than a single application of DPL can be considered for especially recalcitrant telangiectatic cases. The reason we selected 4 weeks after the last session as an appropriate time point for evaluation was that some adverse effects and recurrence that may interfere with the assessment of improvement by dermatologists would have resolved by that time. Adverse effects such as skin flushing, edema and other reactions caused by DPL resolve completely within 4 weeks of the last treatment session. In addition, the recurrence rate, which was measured 4 weeks after the last session, was low [24]. However, the recurrence rate measured at the 6-month follow-up may reach 30% [6].

Our results showed that there were no significant differences in the efficacy of DPL treatment for erythematous and telangiectatic lesions between the 40 years old or younger and those older than 40 years. This result was in accordance with the results reported by Schroeter et al. and Campolmi et al. [19, 25] but differed from the results reported by Lim et al. Lim et al. used IPL and found a better treatment response in patients 40 years old or younger than in those older than 40 years [16]. It was confirmed that the selective absorption of light by water in the tissue could lead to subsequent collagen synthesis and the alleviation of ETR [26]. We found different results because we applied DPL, which covered a much narrower spectrum of wavelengths (500–600 nm) than IPL (540–950 nm). The light absorption by water is greatly reduced at the 500–600 nm wavelength range compared with at the 540–950 nm wavelength range; thus, the conduction of heat to the surrounding collagen was reduced, and the effects on subsequent collagen synthesis and the alleviation of ETR were weakened.

VISIA percentile rankings for red areas of the skin are widely adopted by many dermatologists for the evaluation of treatment efficacy for both erythematous and telangiectatic skin disorders [8, 27]. However, erythema cannot be fully segmented or recognized by VISIA, especially when presenting in a diffuse or graded manner. Some researchers have recommended analysing topical images captured from the same positions with the same size at different time points to exclude bias [28]. However, when lesions of other erythematous or vascular disorders appear within the area being analysed by the VISIA system, e.g. skin lesions of acne, eczema, spider

veins etc., there would be bias in the results of the VISIA percentile rankings. Compared with the results from instrumental evaluations, subjective evaluation results are more similar to the real-world results, and erythema and telangiectasia can be identified and evaluated independently [29]. In our study, although there were significant differences in VISIA percentile rankings after treatment, VISIA percentile ranking was not considered to be a factor reflecting the efficacy of the treatment of ETR with DPL.

We analysed whether the skin lesion sites affected the efficacy of ETR because ETR may be associated with non-visible demodex proliferation [30], and a higher density of demodex has been detected on the forehead and cheeks [31]. We found that there were no significant differences in efficacy among different lesion sites groups. Further investigation should be performed regarding whether *Demodex folliculorum* is related to the efficacy and recurrence of ETR during follow-up.

Limitations

There were some limitations of our study. First, the patients were selected from only one hospital, and multicentre research with a larger sample size and longer follow-up time is needed to obtain more objective and reliable results. Second, limited subjective and objective variables were examined, and other variables, such as the disease duration, the patient's Global Improvement Assessment and Global Flushing Severity Score, were not investigated. Third, the study was retrospective and non-randomized; therefore, prospective research is necessary.

CONCLUSION

The efficacy of DPL for the treatment of ETR was not affected by the severity of erythema, whereas DPL was not as effective at treating severe telangiectasia as it was at treating mild telangiectasia. Further research on alternatives to DPL therapy should be performed to improve the efficacy of treatment for patients with ETR with severe telangiectasia.

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Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole and have given their approval for this version to be published.

Authorship Contributions. Leran Zhao and Cong You carried out the study, participated in collecting data, and wrote the manuscript. Han Chen, Jiangyi Wang and Junya Cao performed the statistical analysis. Manli Qi, Shuping Hou, Xin Zheng, Lili Shao, and Quanzhong Liu designed the study and participated in collecting data. Leran Zhao and Cong You contributed equally to this study and are co-first authors.

Disclosures. Leran Zhao, Cong You, Han Chen, Jiangyi Wang, Junya Cao, Manli Qi, Shuping Hou, Xin Zheng, Lili Shao and Quanzhong Liu have nothing to disclose.

Compliance with Ethics Guidelines. Before undergoing the procedures, all patients provided written informed consent for their photographs and data to be published in the article. The study adhered to the principles of the World Medical Association's Declaration of Helsinki, and ethics approval for this study was granted by the Ethics Committee of Tianjin Medical University General Hospital (No. IRB2020-WZ-093).

Data Availability. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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