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ORIGINAL RESEARCH

Hemoporfin-Mediated Photodynamic Therapy for Port-Wine Stains on Extremities

Jie Kang · Jing-jing Liu · Yu-hong Fang · Yan-yan Lin · Wei Gong · Huai-yu Wang · Li-hang Lin · Xue-min Xiao

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ABSTRACT

Introduction: Pulsed dye laser (PDL) is currently considered to be the first-line treatment for port-wine stains (PWSs) on the extremities despite its less than satisfactory therapeutic efficacy. Hemoporfin-mediated photodynamic therapy (HMME-PDT) is a vascular-targeted therapy that has rarely been used to treat PWSs on the extremities. Here, we evaluate the clinical efficacy and safety of HMME-PDT for the treatment of PWSs on the extremities.

Methods: Clinical data and dermoscopic images of PWSs on the extremities were obtained from 65 patients who underwent HMME-PDT between February 2019 and December 2022. The clinical efficacy of HMME-PDT was analyzed by comparing the pre- and post-treatment images. The safety of HMME-PDT was evaluated through observation during the treatment period and post-treatment follow-up.

Results: The efficacy rate of a single HMME-PDT session was 63.0% and that of two and three to six sessions was 86.7% and 91.3%, respectively. A positive correlation was found between therapeutic efficacy and the number of HMME-PDT sessions. The therapeutic efficacy of HMME-PDT was better on the proximal extremities than on other parts of the extremities ($P = 0.038$), and the efficacy of treating PWSs in each site was relatively improved with an increase of treatment time. The clinical efficacy of HMME-PDT differed across four PWS vascular patterns identified by dermoscopy ($P = 0.019$). However, there was no statistical difference in the therapeutic efficacy based on age, sex, type of PWS, and treatment history ($P > 0.05$), which may be partly attributed to the relatively small sample size or poor cooperation of infant patients. No obvious adverse reactions were observed during the follow-up period.

Conclusions: HMME-PDT is a very safe and effective treatment for PWSs on the extremities.

Jie Kang and Jing-jing Liu have contributed equally to this article and should be considered as co-first authors. Li-hang Lin and Xue-min Xiao have contributed equally to this article and should be considered as co-corresponding authors.

J. Kang · J. Liu · Y. Lin · H. Wang · L. Lin (✉) · X. Xiao (✉)
Department of Dermatology, The Union Hospital–Fujian Medical University, Fuzhou 350001, China
e-mail: 460879404@qq.com

X. Xiao
e-mail: 258260101@qq.com

J. Kang
Department of Dermatology, Dermatology Hospital of Fuzhou, Fuzhou 350001, China

Y. Fang · W. Gong
Key Laboratory of OptoElectronic Science and Technology for Medicine of the Ministry of Education, College of Photonic and Electronic Engineering, Fujian Normal University, Fuzhou 350007, China

Multiple HMME-PDT treatments, lesions located in proximal limbs, and PWSs with type I and IV vascular patterns under dermoscopy were associated with higher efficacy of HMME-PDT. Dermoscopy may help predict the clinical efficacy of HMME-PDT.
Trial Registration No.: 2020KJT085.

Keywords: Dermoscopy; Efficacy analysis; Extremities; Hematoporphyrin monomethyl ether; Photodynamic therapy; Port-wine stains

Key Summary Points

Why carry out this study?

Recent years has seen the increased use of hemoporfin-mediated photodynamic therapy (HMME-PDT) to treat port-wine stains (PWSs) on the fact.

This study aimed at evaluating the clinical efficacy and safety of HMME-PDT in the treatment of PWSs on the extremities.

What was learned from the study?

HMME-PDT is effective and safe for the treatment of PWSs on the extremities.

Multiple HMME-PDT treatments, lesions located in proximal limbs, and type I and IV patterns under dermoscopy were associated with higher efficacy of HMME-PDT.

INTRODUCTION

Port-wine stains (PWSs) are a congenital capillary malformation with no significant sex-related differences [1, 2]. Based on the clinical manifestations, PWSs are divided into three types: pink, purple, and hypertrophic. At the present time, pulsed dye laser (PDL) is the gold-standard treatment for PWSs [3]. About 15% of all patients with PWSs have these capillary malformations on the limbs. With changing times, people are not only concerned about facial beauty but also about the appearance of their limbs. PWSs on the limbs can be accompanied by Klippel–Trenaunay syndrome (KTS) [4, 5] which without prompt treatment can lead to issues such as unequal length of the limbs and soft tissue hypertrophy. PDL as well as other treatments previously or currently in use have been associated with poor outcomes [6, 7], with an effective rate of 44.5% after at least three PDL treatments [7]. Given the relatively low efficacy of existing treatments, it is important to identify treatments that are more effective for PWSs on the extremities.

In 2017, hemoporfin-mediated photodynamic therapy (HMME-PDT) was approved for the treatment of PWSs in China [8]. Hemoporfin, which is a second-generation photosensitizer, has the advantages of strong photoactivity, high photodynamic efficiency, low toxicity, and rapid clearance [9, 10]. PDT utilizes the cytotoxic singlet oxygen generated by the interaction of light, photosensitizer and oxygen to destroy the deformed capillary network, leading to cell death, endothelial damage, thrombosis and vascular occlusion [2, 8, 11]. Most of previous studies have focused on analyzing the efficacy and safety of HMME-PDT in the treatment of facial PWSs, while there are only a few reports on HMME-PDT in the treatment of PWSs on limbs [2, 8, 11–15].

With the development and application of dermoscopy as a non-invasive method to detect vascular diseases, clinicians can use this tool to identify different vascular diseases and predict the therapeutic effect of PDL therapy by identifying different vascular models [16–20]. In the study reported here, we explored the safety and efficacy of HMME-PDT for PWSs on the extremities and attempted to verify the feasibility of the therapy in clinical practice. In addition, we attempted an in-depth analysis of the differences in the efficacy of HMME-PDT according to age and gender of the patient, lesion location, and pattern of capillaries under dermoscopy.

METHODS

Participants

A total of 65 patients (20 male and 45 female patients; age range 1–44 years) with Fitzpatrick

skin type III–IV and clinically confirmed PWSs were recruited from February 2019 to December 2022. The treatment interval was varied from 3 to 12 months, depending on the extinction time of adverse reactions, especially hyperpigmentation. The limbs were categorized according to anatomical position as proximal, middle, and distal, and the lesions were correspondly classified as proximal lesions, middle lesions, distal lesions, and a mixture of these (Fig. 1). Based on the treatment history, the patients were divided into the no treatment and PDL treatment groups. According to the characteristics of the PWS skin lesions, including the color depth and whether it was thickened and deformed, the lesion was divided into pink, purple, and hypertrophic groups. Patients in this study received one to six sessions of HMME-PDT, and for the purpose of the study they were divided into three groups according to the number of treatment sessions (one, two, multiple).

The Ethics Committee of The Union Affiliated Hospital of Fujian Medical University approved the study (No. 2020KJT085). This study was performed in accordance with the Declaration of Helsinki and its later amendments. Informed consent was obtained from all patients or their parents.

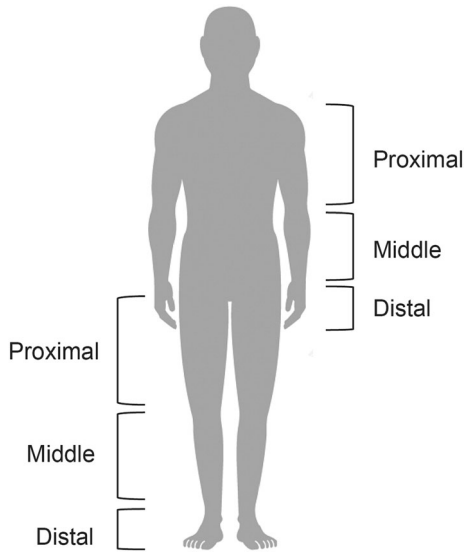

Fig. 1 Anatomical division of the limbs. The limbs are divided into the proximal, middle and distal parts with the wrist, ankle, elbow, and knee joints as boundaries based on the anatomical position and distance from the trunk. Lesions involving different parts are defined as mixed parts

Inclusion and Exclusion Criteria

Patients with PWSs were eligible for inclusion in the study if they met the diagnostic criteria of PWSs, with lesions located in the extremities, and if they had no medical history of another treatment for PWSs, including PDT and PDL, in the past 3 months.

Patients with allergies or other underlying diseases that may have affected the treatment or evaluation were excluded, as were patients with other vascular malformations and vessel-related syndromes and those who were lost to follow-up.

Therapeutic Drugs and Methods

As a first step, the complete area of each lesion was fully exposed and the surrounding normal skin covered. Then, hemoporfin (5 mg/kg; Fudan-Zhangjiang, Shanghai, China) was pumped intravenously into the lesion at a rate of 2.5 mL/min for 20 min. Finally, a 532-nm LED light (Yage, Wuhan, Hubei, China) was used to irradiate (power density: 80–100 mW/cm^2) the lesion, beginning 10 min after the administration of hemoporfin and lasting for 20–25 min.

Dermoscopic assessment

The Canon VEOS handheld dermoscope (Canfield Scientific, Parsippany, NJ, USA) was used to analyze the dermoscopic pattern of different patients. Only when the vascular pattern accounted for 80% of all images in the same PWS can the images of the patient be classified as a specific type. Based on previous studies [21], we focused on three main dermoscopic patterns. The type I pattern represents superficial blood vessels, including point globular and linear blood vessels (Fig. 2a). The type II pattern is mainly reticular blood vessels, representing the deep mode (Fig. 2b). If the images include $\geq$ 2 vascular patterns, it is defined as mixed [22], namely type III (Fig. 2c). The therapeutic effects

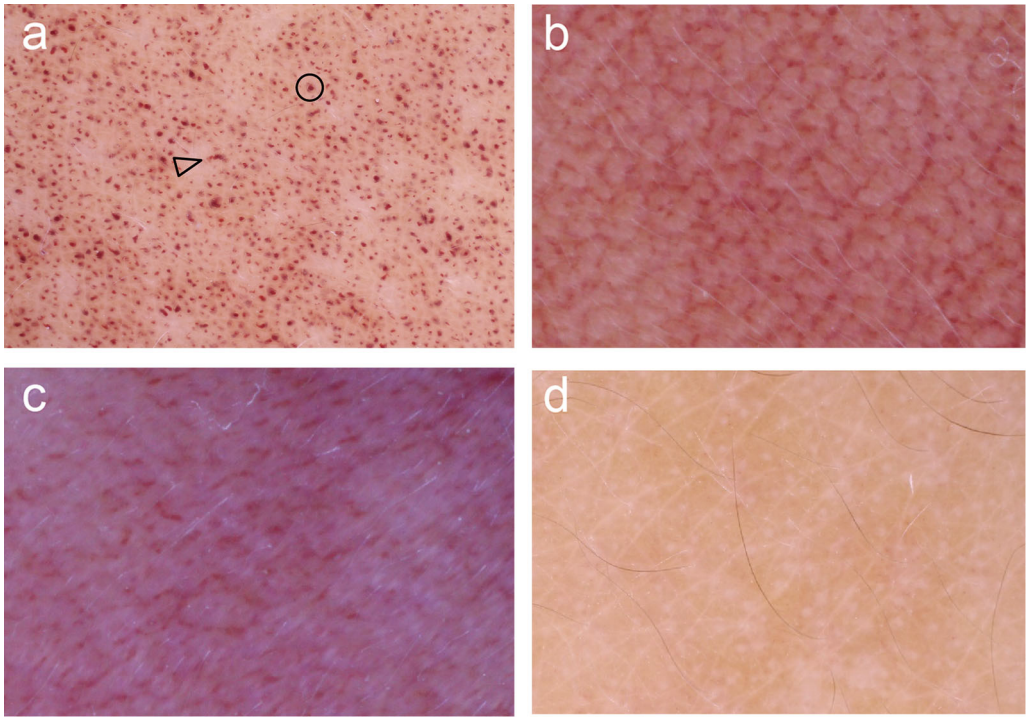

Fig. 2 Different blood vessel types identified by dermoscopy. **a** Type I dermoscopic pattern represents the superficial pattern, including point globular vessels (open circle) and linear blood vessels (open arrowhead). **b** Type II dermoscopic pattern represents the deep pattern, appearing as reticular blood vessels. **c** Type III dermoscopic pattern demonstrates the combined characteristics of the type I and type II patterns. **d** Brown background is fuzzy blood vessels

of single HMME-PDT corresponding to different vascular patterns was analyzed.

Efficacy Criteria

Images of the skin lesions were obtained using a Canon EOS 700D digital camera (Canon, Tokyo, Japan) at the same angle and with the same light source before and after each treatment. Two senior dermatologists who were not involved in the treatment independently compared the changes in skin lesions before and after treatment using a standard classification of quartile percentages (Table 1). Regression values $< 25\%$ were considered to indicate noneffective therapy and values $> 25\%$ were considered to indicate effective therapy. The results were confirmed only when the two doctors reached a consensus. In the event of disagreement, the data were re-evaluated until consensus was reached.

Statistical Analysis

Statistical analysis was performed using SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). Statistical procedures included the Mann–Whitney *U*-test, Kruskal–Wallis *H*-test, χ^2 test, and Spearman correlation analysis. $P < 0.05$ was considered to indicate statistical significance.

RESULTS

Assessment of HMME-PDT Efficacy After One Session

Typical clinical photographs of representative patients before and after one session of HMME-PDT are shown in Fig. 3, and the results of the univariate analysis of the efficacy assessment after one session of HMME-PDT are shown in

Table 1 Standard classification in the response evaluation of port-wine stains

Classification	Degree of improvement	Degree of regression of lesions (%)
1	Poor	0–25
2	Moderate	26–50
3	Good	51–75
4	Excellent	> 75

Table 2. There was no statistical difference in therapeutic efficacy based on age, sex, type of PWSs, and treatment history ($P > 0.05$). The results show that treatment efficacy was related to the distance between the PWSs and the trunk, with the effective treatment rate being 79.2%, 57.1%, 28.6%, and 33.3% for the lesions in the proximal, middle, distal extremities, and mixed parts, respectively ($Z = 8.428$, $P = 0.038$).

When classified according to different dermoscopic categories, eight samples showed the type I vascular pattern (Fig. 4a), with an efficacy rate of 87.5%; 32 samples showed the type II vascular pattern (Fig. 4b), with an efficacy rate

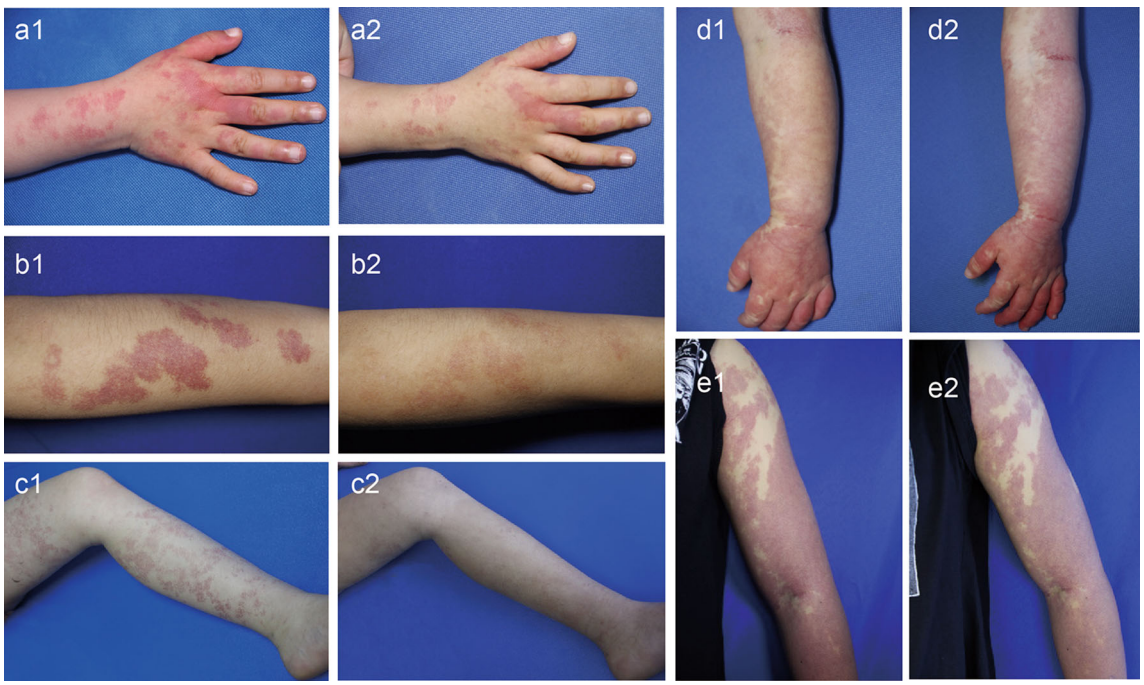

Fig. 3 Representative cases of treatment response after a single session of hemoporfin-mediated photodynamic therapy (HMME-PDT). **a1**, **a2** Port-wine stains (PWSs) on the distal limbs before treatment (**a1**) and after 1 treatment (**a2**), with "good improvement" observed after the treatment. **b1**, **b2** PWSs on the middle limbs before treatment (**b1**) and after 1 treatment (**b2**), with "excellent improvement" observed after the treatment. **c1**, **c2** PWSs on the mixed parts before treatment (**c1**) and after 1 treatment (**c2**), with "excellent improvement" observed after the treatment. **d1**, **d2** PWSs on the mixed parts before treatment (**d1**) and after 1 treatment (**d2**), with "moderate improvement" observed after the treatment. **e1**, **e2** PWSs on the mixed parts before treatment (**e1**) and after 1 treatment (**e1**), with "poor improvement" observed after the treatment

Table 2 Univariate analysis of the efficacy assessment after one session of hemoporfin-mediated photodynamic therapy

Independent variables	Noneffective treatment, *n* (%)	Effective treatment, *n* (%)	Z/χ^2	*P*
Age			19.077	0.580
Sex			0.112	0.573738
Male	8 (12.3)	12 (18.5)		
Female	20 (30.8)	25 (38.5)		
Treatment history			3.494	0.062
None	21 (32.3)	34 (52.3)		
PDL	7 (10.8)	3 (4.6)		
Types of PWSs			3.478	0.062
Pink	15 (23.1)	28 (43.1)		
Purple	13 (20.0)	9 (13.8)		
Hypertrophic	0 (0.0)	0 (0.0)		
Lesion distribution				
Proximal	5 (7.7)	19 (29.2)	8.428	0.038
Middle	12 (18.5)	16 (24.6)		
Distal	5 (7.7)	2 (3.1)		
Mixed parts	4 (6.2)	2 (3.1)		
Vascular pattern				
I	1 (1.5)	7 (10.8)	9.915	0.019
II	22 (33.8)	10 (15.4)		
III	11 (16.9)	6 (9.2)		
IV	3 (4.6)	5 (7.7)		

of 31.3%; and 17 samples showed the type III vascular pattern (Fig. 4c), with an efficacy rate of 35.3%. In addition, there were eight samples that differed from the types described in previous studies: these lesions manifested as a blurred blood vessel shape on a brown background (Fig. 2d) that was similar to the hyperpigmentation pattern of previous treatments. However, these vascular patterns were observed in some patients with PWSs who had never undergone any previous treatment. Even after the resolution was adjusted, it was difficult to identify the pattern; these samples were designated as having the type IV pattern (brown pattern) based on the description by Kwiek et al. (Fig. 4d) [23]. The efficacy rate of the treatment on this pattern was 62.5%. Dermoscopy revealed that the clinical efficacy of the treatment differed for each of the four vascular patterns ($Z = 9.915$, $P = 0.019$).

Assessment of the Efficacy of Different Numbers of HMME-PDT Sessions

The patients were divided into three groups according to the number of sessions of HMME-PDT and statistical analyses were performed (Table 3). A total of 27 patients only completed

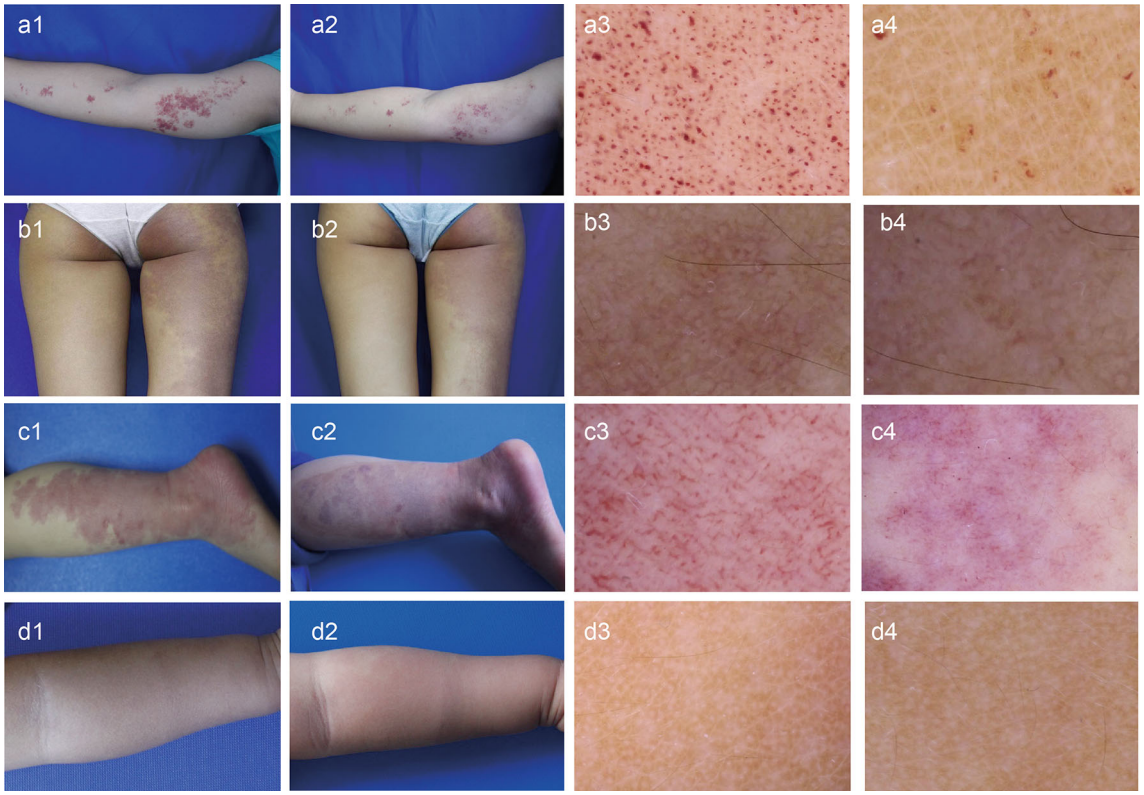

Fig. 4 Representative PWS cases evaluated by dermoscopy before and after 1 session of HMME-PDT. **a1–d1** Clinical photographs obtained before HMME-PDT. **a2–d2** Clinical photographs obtained after HMME-PDT. **a3–d3** Dermoscopic images before HMME-PDT. **a4–d4** Dermoscopic images after HMME-PDT. **a1–a4** The type I vascular pattern, with "excellent improvement"; **b1–b4** the type II vascular pattern, with "moderate improvement"; **c1–c4** the type III vascular pattern, with "poor improvement"; **d1–d4** the type IV vascular pattern with "good improvement" after HMME-PDT

a single session of HMME-PDT, with the effective rate of 63.0%; 15 patients underwent two sessions, with the effective rate of 86.7%; and 23 patients underwent three to six sessions, with the effective rate of 91.3%. The efficacy of HMME-PDT differed depending on the number of sessions ($\chi^2 = 6.577$, $P = 0.037$, Kruskal–Wallis *H*-test). A bivariate correlation analysis was performed ($r_s = 0.308$, $P = 0.013$, two-sided Spearman test), which revealed that there was a positive correlation in the efficacy between different sessions of HMME-PDT. Typical clinical photographs of representative patients before and after undergoing different numbers of sessions of HMME-PDT are shown in Fig. 5.

With increasing treatment time, the efficacy of the treatment in lesions located in different parts of the limbs also improved by varying degrees. The efficacy of treatment in the proximal extremity increased from 79.2% to 100.0%; that in the middle proximal extremity, from 57.1% to 92.3%; that in the distal extremity, from 28.6% to 66.7%; and that in the mixed parts, from 33.3% to 66.7% (Table 4).

Safety

Most of the patients with PWSs experienced pruritus, burning, and pain during the treatment. Some patients showed blisters, scabs, hyperpigmentation, scars, and other skin reactions in the treated areas after HMME-PDT (Fig. 6). Data analysis is shown in Table 5. Most skin reactions subsided naturally within 1 week to 1 month after the treatment session, but hyperpigmentation could last for 3–6 months.

Table 3 Efficacy assessment of hemoporfin-mediated photodynamic therapy in patients receiving different numbers of sessions

Number of treatments	Total *n* (%)	Noneffective treatment, *n* (%)	Effective treatment, *n* (%)	Efficacy rate (%)
1	27 (41.5)	10 (15.4)	17 (26.2)	63.0
2	15 (23.1)	2 (3.1)	13 (20.0)	86.7
3–6	23 (35.4)	2 (3.1)	21 (32.3)	91.3

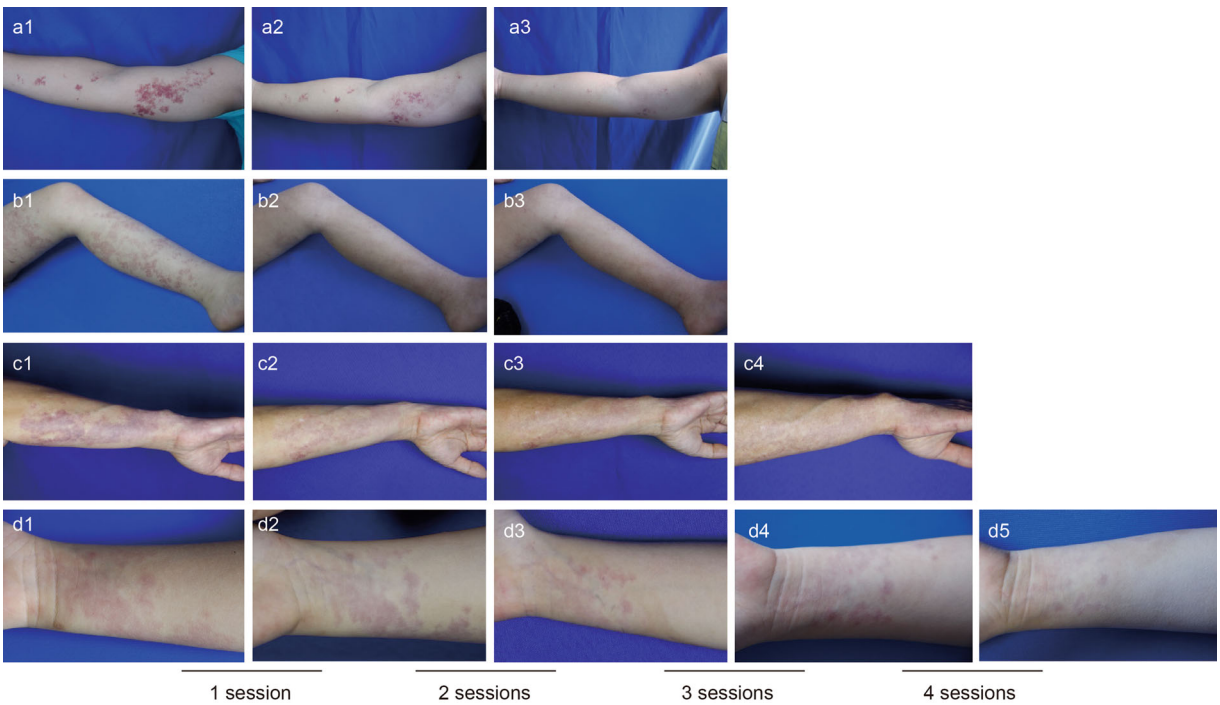

Fig. 5 Representative cases of the treatment response after multiple sessions of HMME-PDT. There was a positive correlation between PWS regression and increasing number of HMME-PDT sessions

Routine blood, liver function, and kidney function tests, as well as electrocardiogram, revealed no obvious abnormalities in all patients at 3–6 months following HMME-PDT.

DISCUSSION

Photodynamic therapy destroys malformed capillaries in PWSs by selective photothermolysis and improves the appearance of patients with PWSs. As the gold standard, PDL is widely performed for the treatment of PWSs on the extremities; however, it is associated with disadvantages, such as low therapeutic efficacy [7, 24]. In addition, patients may experience adverse reactions, such as discoloration of the skin and scarring. Compared with the blood vessels of the face, those in the extremities are smaller in diameter [25], and there are more vellus hairs in the limbs. The blood vessels of PWSs in the limbs may penetrate through the hair follicles into the deep dermis, resulting in the malformed PWS blood vessels being located relatively deeper in the extremities [26], which may complicate treatment.

Table 4 Efficacy assessment after different numbers of sessions of hemoporfin-mediated photodynamic therapy according to anatomical position of lesions in the extremities

Anatomical position	One session			Two sessions			Three to six sessions		
	Noneffective treatment, *n* (%)	Effective treatment, *n* (%)	Efficacy rate (%)	Noneffective treatment, *n* (%)	Effective treatment, *n* (%)	Efficacy rate (%)	Noneffective treatment, *n* (%)	Effective treatment, *n* (%)	Efficacy rate (%)
Proximal	5 (7.7)	19 (29.2)	79.2	1 (2.6)	12 (31.6)	92.3	0	4 (17.4)	100
Middle	12 (18.5)	16 (24.6)	57.1	3 (7.9)	14 (36.8)	82.4	1 (4.3)	12 (52.2)	92.3
Distal	5 (7.7)	2 (3.1)	28.6	3 (7.9)	2 (5.3)	40.0	1 (4.3)	2 (8.7)	66.7
Mixed parts	4 (6.2)	2 (3.1)	33.3	1 (4.3)	2 (5.3)	66.7	1 (4.3)	2 (8.7)	66.7

In this study, the efficacy rate of a single session of HMME-PDT was 63.0% and that of multiple sessions (2–6 sessions) was as high as > 85%, which was better than that of PDL on the extremities. The possible reasons for the higher efficacy of HMMR–PDT may include the following: (1) PDT can target capillaries of all diameters and has a higher penetration depth than PDL [27]; (2) in contrast to PDL, which acts only through photothermal dissolution, PDT can simultaneously destroy expanded blood vessels through intravascular photochemical and photothermal reactions [13]; (3) In PDL treatment, epidermal melanin demonstrates a strong competitive absorption of light, which weakens the therapeutic efficacy [27]; and (4) abnormal overexpression of vascular endothelial growth factor (VEGF) in patients with PWSs [14], which leads to vascular proliferation and vasodilatation. It should be noted that PDL can upregulate the expression of VEGF by post-treatment regeneration and revascularization of blood vessels [28] and HMME-PDT can down-regulate the expression of VEGF [9], thereby resulting in apoptosis of the endothelial cells and occlusion of dilated capillaries in the PWSs.

Factors such as age, sex, type of PWSs, and treatment history did not affect the therapeutic efficacy in this study. However, previous studies have shown that the progression and treatment response of PWSs are closely related to age [7, 29, 30]. In general, the response of children to PDT should be better than that of adults due to the former having thinner skin and shallower surface blood vessels [15, 31]. That our results are inconsistent with those of previous studies can be attributed to the relatively small sample size in this study or poor cooperation of infant patients. There was no statistical difference in the efficacy of HMME-PDT between patients with or without a history of PDL on the extremities, which is consistent with the results of a study carried out on the face and neck [32]. The results indicate that the efficacy of HMME-PDT is not affected by a history of regular PDL treatments. However, significant perivascular fibrosis and scarring resulting from irregular treatment may affect the efficacy of subsequent PDT [32].

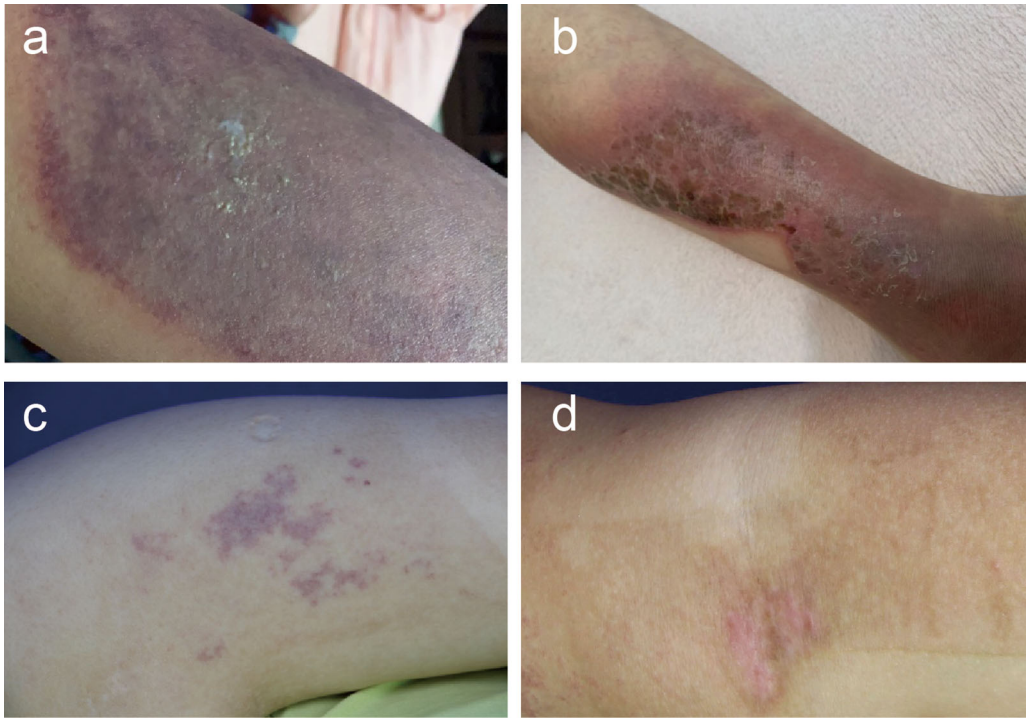

Fig. 6 Treatment response and adverse reactions following HMME-PDT. **a** Needle tip-sized blisters in the treatment area 24 h after HMME-PDT, **b** scabs formed 7 days after HMME-PDT, **c** hyperpigmentation after HMME-PDT, **d** hyperpigmentation and superficial scar formation 3 months after HMME-PDT

Table 5 The incidence of postoperative adverse reactions

Adverse reactions	None, *n* (%)	Incidence of postoperative adverse reactions, *n* (%)			
		Total	Mild	Moderate	Severe
Pruritus	5 (7.7)	60 (92.3)	54 (83.1)	5 (8.0)	1 (1.5)
Burning	0 (0.0)	65 (100.0)	44 (67.7)	21 (32.3)	0 (0.0)
Pain	0 (0.0)	65 (100.0)	24 (36.9)	20 (30.8)	21 (32.3)
Localized edema	17 (26.2)	48 (73.8)	46 (70.8)	2 (3.1)	0 (0.0)
Small blisters	55 (84.6)	10 (15.4)	7 (10.8)	2 (3.1)	1 (1.5)
Scab	45 (69.2)	20 (30.8)	17 (26.2)	2 (3.1)	1 (1.5)
Hyperpigmentation	38 (58.5)	27 (41.5)	19 (29.2)	7 (10.8)	1 (1.5)
Hypopigmentation	64 (98.5)	1 (1.5)	1 (1.5)	0 (0.0)	0 (0.0)
Infection	62 (95.4)	3 (1.5)	1 (1.5)	2 (3.1)	0 (0.0)
Scar	63 (96.9)	2 (3.1)	1 (1.5)	1 (1.5)	0 (0.0)
Photosensitive reaction, Systemic symptoms	65 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

The efficacy of HMME-PDT is related to the photosensitizers, singlet oxygen, and irradiation light sources. Factors that may affect these variables may lead to differences in the therapeutic efficacy of the treatment [33, 34]. We suggest that the following factors be considered as accounting for the enhanced efficacy of HMME-PDT in proximal extremities compared to the middle and distal ends. First, the epidermis and stratum corneum of the distal extremities are thicker than those of the proximal and middle ends, as shown by Yu et al. [6] in pathological examinations. This increase in epidermal thickness may lead to stronger scattering and absorption [6], thereby affecting the therapeutic outcome. Second, the penetration depth of the 532-nm light source is limited while the blood vessels of the distal limbs are deeper than those of the proximal limbs [6]. Under the same light source, the blood vessels of the distal limbs absorb less light than the proximal end. Third, the currently used PDT light source is flat, which cannot completely cover the distal skin lesions located on the curved surface of the limbs. Fourth, the oxygen content of the middle and distal limbs is relatively low due to gravity or deoxygenation in the blood circulation [29], which affects the amount of singlet oxygen produced during PDT. Fifth, the distal limbs could not be stabilized in some pediatric patients owing to a burning sensation and pain during the treatment, resulting in the reduction of energy delivered to the skin lesions of the distal limbs.

Dermoscopy can objectively reflect the characteristics of malformed blood vessels in PWSs by partially magnifying the skin lesions. The authors of some studies have reported associations between the dermoscopic vascular patterns and histopathology of facial PWSs as well as PDT efficacy [25, 35]. In this study, lesions of the type I vascular pattern demonstrated a higher efficacy rate, as evidenced by dermoscopy, while those with the type II and type III patterns showed a lower efficacy rate; these results are consistent with those of previous studies [36]. In lesions with the type I pattern, the wall of deformed blood vessels is thin, and the majority of blood vessels are located in the superficial dermis, perpendicular to the skin [21–23, 36]. The PDT light source can easily penetrate the vascular endothelial cells and destroy the blood vessels and, consequently, the lesions respond well to treatment [16]. In comparison, in lesions with the type II pattern, the blood vessels are located in the deeper part of the dermis [16, 21–23], and are intertwined, overlapped and arranged tightly. The walls of these blood vessels are thick, and the surrounding collagen fibers are closely arranged. These factors significantly affect the penetration of the 532-nm light source. Therefore, for deeply located PWSs and lesions with a large diameter or hyperplasia, it is reasonable to increase the irradiation energy or use a light with a higher wavelength (755/1064 nm) [25]. However, it is important to be wary of serious adverse reactions, such as severe collagen rearrangement and scarring. Lesions of the type III are a mixed pattern, demonstrating the characteristics of both type I and type II patterns; therefore, the curative effect of PDT in our study was also intermediate.

The curative effect of PDT on lesions of the type IV pattern was higher than that on lesions of the type II and III patterns, but lower than that of lesions with the type I pattern. The vague blood vessel shape seen in this pattern suggests that it may not be a superficial blood vessel pattern. Short-wavelength light with limited penetrating power cannot completely destroy the malformed blood vessels. Therefore, the therapeutic effect of HMME-PDT on lesions of the type IV pattern was marginally worse than that on lesions of the superficial patterns. Optical coherence tomography and other techniques can be used to confirm the depth of the blood vessels in this pattern [37]. Future studies on large samples should be performed to explore the relationship between this pattern and the efficacy, with the ultimate aim to clarify whether the brown pattern can be considered an independent entity and whether it is worth promoting clinically. Dermoscopy can be performed prior to the first HMME-PDT to distinguish the four vascular patterns of PWSs, thereby helping to predict the efficacy of HMME-PDT and assist in managing the treatment parameters and expectations of patients.

The number of sessions of HMME-PDT is directly proportional to its efficacy. In most of our patients, multiple sessions resulted in better outcomes, even in the distal part where HMME-PDT had relatively poor efficacy. In a small number of patients, the skin lesions did not improve significantly after three sessions of HMME-PDT but showed definite improvement during next sessions, suggesting that HMME-PDT might have a cumulative effect [14]. Therefore, we recommend that patients receive a course of HMME-PDT (3–5 sessions) to evaluate the efficacy of the treatment. However, some patients who underwent $\geq$ 4 sessions of HMME-PDT did not demonstrate any obvious changes; such patients may be considered to show treatment resistance. Unfortunately, the treatment endpoint could not be clarified in this study. Further research is warranted to provide reference indicators to determine treatment endpoints.

In this study, no serious adverse reactions were observed during the follow-up, which proved the safety of HMME-PDT on the extremities. Some patients develop hyperpigmentation, which may be caused by the destruction of melanocytes and/or post-inflammatory changes [31]. Since the duration of hyperpigmentation of the limbs is longer than that of the face, the treatment interval for PWSs in the limbs should be appropriately extended. Choosing the appropriate irradiation power and irradiation time according to the patient's skin type and previous treatment response, as well as close observation of the local responses and endpoint can help reduce the occurrence of hyperpigmentation. In addition, due to insufficient cold compress, three patients had moderate to severe scabs, two of whom were left with permanent scars. Therefore, intermittent cold compress should be enforced during this period of postoperative swelling, and direct strong sunlight should be avoided until the hyperpigmentation fades, so as to reduce the side effects of treatment and achieve a better therapeutic effect.

A pharmacokinetic study on HMME revealed that the plasma concentration reached its peak 20 min after administration and began to drop sharply 30 min post-administration [38]

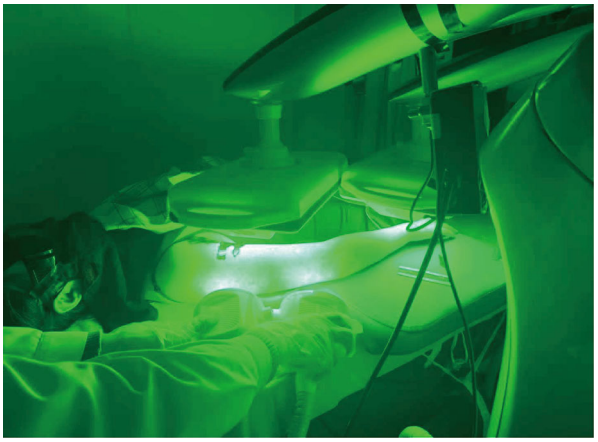

Fig. 7 Image of the treatment of large PWSs on extremities. Two sets of 532-nm light sources were used to irradiate large PWSs on the limbs simultaneously

Therefore, the best time to irradiate is 10–30 min after the administration of HMME. Some patients tend to have large skin lesions; however, the area of the light source is generally limited (large spot: 10 $\times$ 10 cm; small spot: 5 $\times$ 5 cm). Single irradiation with single piece of equipment cannot cover all skin lesions. Therefore, we used two sets of large light sources for simultaneous irradiation after obtaining informed consent from the patient (Fig. 7). No obvious adverse reactions were observed during or after the treatment. The PWSs subsided evenly after 3–6 months, and there were no abnormalities in results from routine blood tests, liver and kidney function tests, and other indicators. However, the safety of combined treatment with multiple light sources needs to be verified in further studies.

To our knowledge, this is the first study with a relatively large sample focusing on the treatment of HMME-PDT for PWSs on the extremities. Collectively, HMME-PDT is effective and safe for the treatment of PWSs on the extremities, especially on proximal limbs. The efficacy was enhanced with an increase in the number of treatment sessions. In addition, this study found that there were differences in the efficacy of treatment according to the different vascular patterns, suggesting that vascular pattern could be used as a marker to predict clinical efficacy. The limitations of the current study are the

relatively small sample size and the lack of a control group. Future studies should have a larger sample to further explore the relationship between the clinical efficacy of HMME-PDT and external variables and to compare the efficacy of HMME-PDT and PDL for the treatment of PWSs on the extremities.

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Disclosures. Jie Kang, Jing-jing Liu, Yu-hong Fang, Yan-yan Lin, Wei Gong, Huai-yu Wang, Li-hang Lin, and Xue-min Xiao declare that they have nothing to disclose.

Compliance with Ethics Guidelines. This study was approved by the Ethics Committee of the the Union Hospital of Fujian Medical University. This study was performed in accordance with the Helsinki Declaration and its later amendments. Informed consent was obtained from all participants and/or their parents for possible publication of their digital photographs.

Data Availability. The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

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