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ORIGINAL RESEARCH

Clinical Observation on the Therapeutic Effect of Port-Wine Stains with Intravenous Injection of Hematoporphyrin Monomethyl Ether (HMME)

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Background: Hematoporphyrin monomethyl ether (HMME) is a promising photosensitizer for photodynamic therapy (PDT) and has found wide application in the treatment of port-wine stains (PWS).

Objective: This study aims to observe and analyze the clinical efficacy and safety of HMME-PDT in the treatment of PWS patients. It also aims to evaluate the usefulness of color Doppler flow imaging (CDFI), an ultrasound technique for detecting blood flow in skin lesions, in assessing clinical efficacy.

Methods: Thirty-three patients with PWS underwent HMME-PDT at our dermatology outpatient clinic between January 2019 and March 2020. Data on patient demographics, lesion location, lesion type (pink, purple, nodular thickening), treatment frequency, and pre- and post-treatment images were collected and retrospectively analyzed. CDFI was performed on three patients.

Results: All patients received intravenous HMME and underwent irradiation with 532 nm green LED light. Of these, 5 patients received 1 session of HMME-PDT, 14 received 2 sessions, 9 received 3 sessions and the remaining 5 patients received more than 3 sessions. Of the 33 patients, 9 were cured (27.27%), 10 showed improvement (30.30%), 11 experienced a reduction in symptoms (33.33%), and 3 showed no significant improvement (9.09%). Most patients reported local pain and oedema, and no systemic adverse effects were observed. Clinical efficacy correlated with lesion type and total number of treatment sessions. CDFI appears to be an excellent technique for assessing clinical efficacy.

Conclusion: HMME-PDT is a safe and effective method for the treatment of PWS. CDFI examination appears to be a promising assessment tool. However, further validation with larger sample sizes is warranted.

Keywords: port-wine stains, hematoporphyrin monomethyl ether, photodynamic therapy, color Doppler flow imaging

Introduction

Port-wine stains (PWS) are congenital slow-flow vascular malformations of the skin characterized by progressive dilatation of a superficial cutaneous vascular plexus.[1] PWS affects approximately 0.3–0.6% of newborns and typically manifests on the face and neck. The male to female ratio is 1:1. Initially, PWS presents as irregular red macules that progress over time to dark purple, hypertrophic and nodular lesions.[2] The histopathological features of PWS are the ectatic capillaries in the papillary dermis without vascular endothelial proliferation, and in severe cases may also occur in the reticular dermis and hypodermis. The absence of normal arterioles and venules in lesions is probably due to the coexistence of EphB1and ephrinB2 in endothelial cells, disrupting intercellular communication and causing progressive vascular dilation. A recent study showed variable histopathological abnormalities in PWS lesions in infants and young children, including changes in pericyte and basement membrane thickness, smooth muscle degeneration, and disorganization and hypertrophy of collagen and elastic fibers. These abnormalities may be closely associated with genetic mutations, including Gα-subunit Q (GNAQ), phosphatidylinositol 3-kinase, EPHA3, c-Myb and β-platelet-derived growth factor receptor.[3]

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PWS lesions progress gradually with age, potentially resulting in disfiguring, asymmetric and spontaneous bleeding. The cosmetic deformity severely impact patients' psychological health and quality of life.[4] Therapies for PWS include cosmetic camouflage, skin grafting, radiation, cryosurgery, dermabrasion, tattooing and electrotherapy. However, pulsed dye laser (PDL) therapy is the current gold standard for the treatment of PWS, albeit with a cure rate of less than 10%.[5] In 1991, Prof. Gu Ying's team at the People's Liberation Army General Hospital in China pioneered using PDT for the treatment of PWS, and achieved remarkable efficacy, especially for large and thick lesions.[6] The mechanism involves the elimination of pathological dilated blood vessels by inducing apoptosis of abnormal vascular endothelial cells, triggering tissue inflammation, immune response, fibrosis and vascular occlusion through a series of biochemical reactions between photosensitizers and oxygen molecules in the lesion tissue. Previous studies suggest that hematoporphyrin monomethyl ether (HMME) is a promising photosensitizer for PDT due to its potent photodynamic effect and widespread use in the clinical treatment of vascular malformations.[7] Therefore, we aim to evaluate the efficacy and safety of HMME-PDT for the treatment of PWS in Chinese patients, to investigate potential factors affecting clinical efficacy, and to evaluate therapeutic outcomes using colour Doppler flow imaging (CDFI) to compare blood flow classification and skin thickness before and after treatment.

Methods

Patients

Thirty-three patients treated with HMME-PDT for PWS at our dermatology outpatient clinic between January 2019 and March 2020 were included. Data on patient demographics, lesion locations, lesion types (pink, purple, nodular thickened), treatment sessions, and pre- and post-treatment images were collected and retrospectively analyzed.

Prior to enrollment, all patients underwent blood tests, urine tests, and liver and kidney function tests to exclude significant physical illness. Patients with a history of isotope, laser or PDT therapy, systemic treatment within the previous 4 weeks or local treatment within the previous 2 weeks were excluded. Patients with other vascular malformations, vascular-related syndromes, allergy to porphyrin and its analogs, photosensitivity, porphyria, scarring, organic heart disease, coagulopathy, mental illness, severe endocrine disease, current or recent history of drug treatment, or photosensitivity were also excluded.[8]

Ethical Statement

The study was conducted in accordance with the Declaration of Helsinki, and was approved by the Research Ethics Committee of the Third Affiliated Hospital of Soochow University (2017–045). All patients and/or their legal guardians were informed about the purpose of the study, the treatment method, etc., and signed the informed consent form. And the patients and/or their legal guardian(s) gave their permission for the images to be published.

Procedure for HMME-PDT

Pre-Treatment Skin Test

HMME was dissolved in 10 mL normal saline, and 0.1mL of this solution (containing 10 mg of HMME) was added to 8 mL of normal saline to give a concentration of 125 mg/mL. A 0.1 mL aliquot of the diluent was then injected subcutaneously into the inner side of either the left or right forearm, while normal saline was injected into the opposite side as a control. Skin test reactions were observed 20 minutes later, and only patients with negative skin test results were eligible for HMME-PDT treatment.

Pre-Treatment Preparation

Photograph each patient's PWS lesion and record their details. Measure each patient's weight and calculate their photosensitizer dose based on their weight (5mg/kg). Troubleshoot the equipment to ensure it is working normally. Apply medical adhesive plasters around the edge of the treated area prior to treatment. Cover normal skin outside the treated area with a double layer of black cloth. Fully expose the irradiated area, keeping it as much as possible in the same plane as the treated area.

Intravenous Injection of HMME

Connect the photosensitiser and normal saline with a three-way device. Slowly inject the photosensitiser over 20 minutes after successful venipuncture, then wash the channel with normal saline to ensure the drug has completely entered the blood vessels.

Light Therapy

The interval between the start of intravenous administration and the start of light exposure was 10 min. Maintain the irradiation plane vertical to the treated area using a 532 nm green LED light (produced by a Wuhan YaGe LED-IE device), paying close attention to changes in the irradiation area and the output dose of the device. Set the irradiation dose at 85–95 mW/cm^2 and the treatment time at 20 min to achieve an energy density of 110–120 J/cm^2. Take full account of the patient's skin condition, age and other factors when choosing the dose and duration of treatment. Eye protection should be used during treatment. Monitor the response of the treatment area to avoid over-irradiation in real-time. Treatment is completed when purpura-like changes appear on the lesions and should be interrupted if there is any pain or other discomfort during this time.

Precautions After Treatment

Redness and oedema can be relieved with cold sprays or wet compresses immediately after each treatment and for the first few days afterwards. Exposure to light should be avoided for 2 weeks. Wear protective clothing and sunglasses if exposed to light. Moisturizers may be used to reduce the dryness of lesions after treatment. Scabs should be allowed to dry and fall off naturally to prevent infection from friction or collision. Cosmetics or treatments containing irritating ingredients such as alpha-hydroxy acid and salicylic acid should be avoided during therapy.

Color Doppler Flow Imaging (CDFI)

The color Doppler flow imaging (CDFI) was performed by the same radiologist with more than three years of experience in ultrasound. The device used to acquire the images was a persona 70b from the company Mind ray. The imaging assessments of all patients were performed by two sonographers with at least 10 years of experience. The CDFI assesses the quantity, morphology and distribution of the vessels. Cases were graded according to the ADLER's method as absent (grade 0), minimal (grade 1), moderate (grade 2) or marked (grade 3). The higher the grade, the more abundant the blood flow. Compare the difference in blood flow classification and thickness before and after treatment.

Clinical Efficacy Evaluation

Patients were treated every two to four months. After one to five treatments, efficacy was evaluated by senior dermatologists in our department by comparing each patient's pre- and post-treatment photographs taken under a fixed light source. Standards used to evaluate efficacy: Cured: Colour had largely faded in the treated area (degree of improvement $\geq$ 90%); Good: Color had significantly faded in the treated area (improvement $\geq$ 60%, $<$ 90%); Moderate: The colour in the treated area had partially faded (degree of improvement $\geq$ 20%, $<$ 60%); None: Colour was mostly unchanged in the treated area (improvement $<$ 20%). Images were taken using the same camera, background, light source and angle.

Statistical methods

Statistical software SPSS22.0 was used for data analysis. Fisher's exact tests were used to compare response rates between groups. A $p< 0.05$ was considered statistically significant.

Results

Clinical Information

Thirty-three patients, aged 2 to 41 years, including 11 males and 22 females, participated in the study. Of these, 30 had lesions on the face and neck and 3 had lesions on the limbs. The lesions were categorized into 15 cases of pink type, 9 cases of purple type and 9 cases of nodular thickening type based on their colour and thickness. Nineteen patients received less than three treatments, whereas 14 patients received three or more treatments (Table 1).

Table 1 Demographic Characteristics of the Patients with PWS

Characteristics	Number of Cases (%)
Gender	
Female	22 (66.67)
Male	11 (33.33)
Age	
<18	16 (48.48)
≥18	17 (51.52)
Location of PWS	
Located on head or neck	30(90.91)
Located on extremity	3(9.1)
Subtype of PWS	
Pink type (I and II)	15(45.46)
Purple type (III)	9(27.27)
Nodular thickening type (IV)	9(27.27)
Number of treatments	
<3	19(57.58)
≥3	14(42.42)

Clinical Efficiency

After multiple treatments with HMME-PDT, 9 out of 33 cases of PWS were cured (27.27%), 10 cases showed good efficacy (30.30%), 11 cases showed relief (33.33%) and 3 cases showed no efficacy (9.09%), resulting in a combined response rate of 57.57% for cure and good efficacy. The efficacy of HMME-PDT in treating PWS in multiple patients is illustrated in Figures 1–4. No significant difference in the response rate was observed between male and female patients ($p = 0.459$), between minors and adults ($p = 0.296$) or between different sites of PWS ($p = 0.244$). However, the cured and good response rate was significantly higher in the pink type than in the purple and nodular thickening types ($p = 0.033, < 0.05$). Furthermore, patients who received three or more sessions had a significantly higher response rate than those who received less than two sessions ($p = 0.001, < 0.05$). In particular, purple and nodular thickening types who received three or more sessions showed better therapeutic efficacy ($p=0.002, <0.05$) (Table 2).

Color Doppler Flow Imaging (CDFI)

CDFI is a well-established non-invasive method for assessing angiogenesis with extensive clinical applications in various vascular diseases.[9] In the later stage of our research, we recognized the potential benefits of assessing the efficacy of

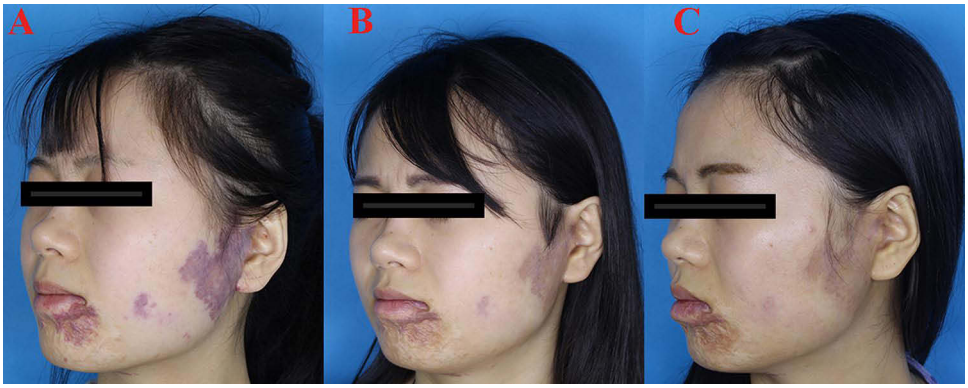

Figure 1 (**A**) Purple type of PWS with scarring in the left mandibular and preauricular region before treatment, (**B**) good efficacy after 2 sessions, (**C**) the lesions were almost cured after 3 sessions.

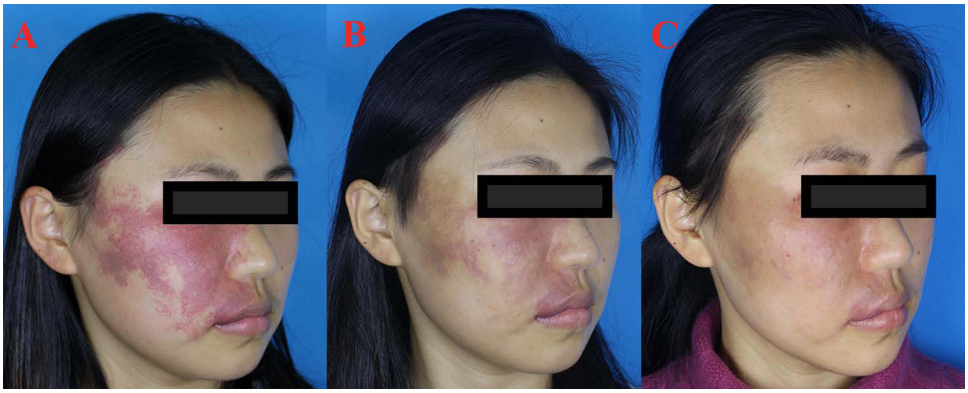

Figure 2 (**A**) A pink type of PWS on the right side of the face before treatment, (**B**) significant cosmetic improvement after 3 sessions, (**C**) the lesions were basically cured after 5 sessions.

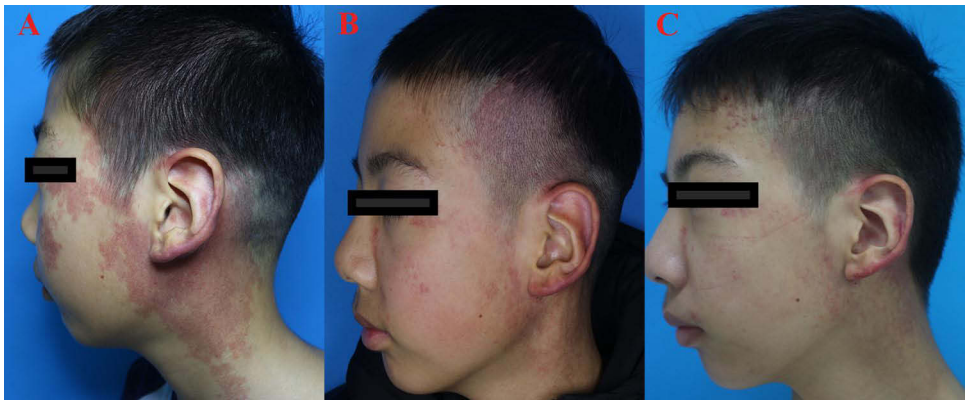

Figure 3 (**A**) A pink type of PWS in the left temporal and neck before treatment, (**B**) got significantly cosmetic improvement after 2 sessions, (**C**) the lesions were mostly cured after 3 sessions.

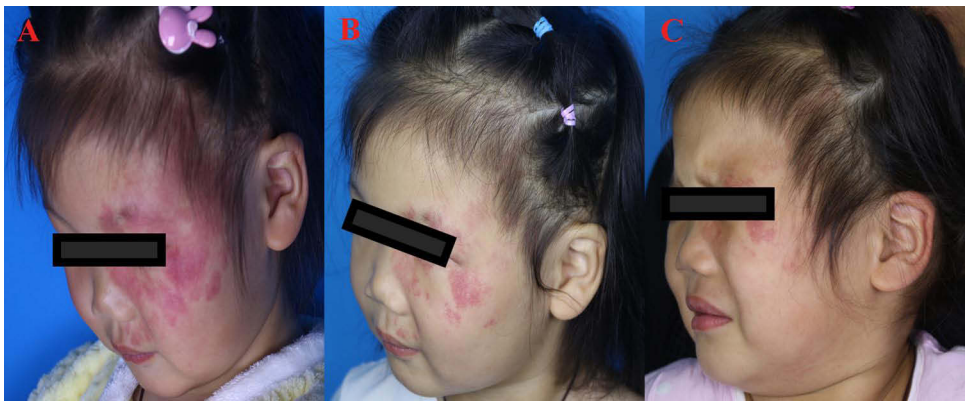

Figure 4 (**A**) A pink type of PWS in the left side of the left temporal, orbital condyle and cheeks before treatment, (**B**) got significantly cosmetic improvement after 2 sessions, (**C**) the lesions subsided about 80% after 3 sessions.

HMME-PDT in PWS using CDFI. Consequently, we performed CDFI studies on the last three patients with PWS. The results showed a significant reduction in blood flow classification and skin thickness after HMME-PDT treatment. In addition, three patients showed varying degrees of reduced skin thickness after treatment (Figure 5).

Table 2 Observation on the Efficacy of HMME-PDT in the Treatment of PWS

	Number of cases	A: Cured, n (%)	B: Good, n (%)	A+B, n (%)	C: Alleviated, n (%)	D: None, n (%)	C+D, n (%)	*p*
Gender								0.459
Female	22	6(27.27)	8(36.37)	14(63.64)	6(27.27)	2(9.09)	8(36.36)	
Male	11	3(27.27)	2(18.18)	5(45.45)	5(45.45)	1(9.09)	6(54.55)	
Age								0.296
<18	16	5(31.25)	6(37.50)	11(68.75)	4(25.00)	1(6.25)	5(31.25)	
≥18	17	4(23.53)	4(23.53)	8(47.06)	7(41.18)	2(11.76)	9(52.94)	
Location of PWS								0.244
Located on head or neck	30	9(30.00)	7(23.33)	16(53.33)	11(36.67)	3(10.00)	14(46.67)	
Located on extremity	3	0(0.00)	3(100.00)	3(100.00)	0(0.00)	0(0.00)	0(0.00)	
Subtype of PWS								0.033
Pink type	15	5(33.33)	7(46.67)	12(80.00)	3(20.00)	0(0.00)	3(20.00)	
Purple type	9	2(22.22)	1(11.11)	3(33.33)	4(44.45)	2(22.22)	6(66.67)	
Nodular thickening type	9	2(22.22)	2(22.22)	4(44.44)	4(44.45)	1(11.11)	5(55.56)	
Number of treatments								0.001
<3	19	1(5.26)	5(26.32)	6(31.58)	10(52.63)	3(15.79)	13(68.42)	
≥3	14	8(57.14)	5(35.72)	13(92.86)	1(7.14)	0(0.00)	1(7.14)	

Treatment-Related Adverse Events

During treatment, 29 cases experienced varying degrees of burning and pain in the treated areas. Patients with severe pain were able to continue treatment after suspension or cold spraying. After treatment, 14 cases experienced varying degrees of oedema, peaking 2–3 days after treatment. In addition, 6 cases developed dark purple spots or black patches, while 3 cases developed eschar, requiring strict care to prevent infection and scarring. Furthermore, Hyperpigmentation of the treated area occurred in 2 cases and resolved spontaneously after 2 months. No other significant systematic adverse events were observed.

Discussion

Port-wine stains (PWS) are vascular birthmarks, primarily on the face and neck, resulting from abnormal embryonic vascular development. PWS typically worsen with age and do not spontaneously resolve. In addition, some patients may present with other vascular malformations, such as Sturge-Weber syndrome and Klippel-Trenaunay syndrome, which

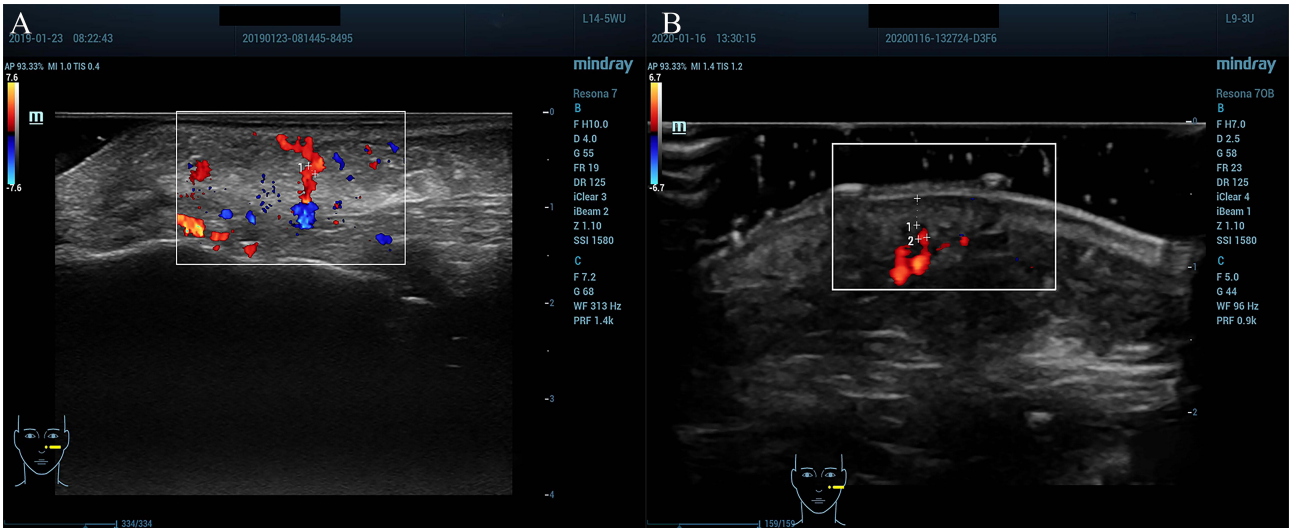

Figure 5 Evaluation of vascularity in lesions by colour Doppler flow imaging (CDFI) before (**A**) and after (**B**) treatment.

significantly affect mental health and overall quality of life.[10] Therefore, there is a need to find effective treatments for PWS. Various treatment modalities for PWS have been used, including cosmetic cover-up, skin grafting, radiation, dermabrasion, cryosurgery, tattooing and electrotherapy, but none have provided cosmetically satisfactory results.[11] Currently, PDL therapy is considered the gold standard for the treatment of PWS due to its ability to obliterate cutaneous vessels with minimal damage to overlying tissues.[12]

While most patients respond to PDL therapy, complete eradication of PWS is rarely achieved. In particular, blue-violet, hypertrophic PWS does not respond well to PDL treatment.[13] In the 1990s, Chinese clinicians began treating PWS with vascular-targeted PDT. Various photosensitizers have been used to treat PWS, including hiporfin, photocarcinorin (PsD-007), hemoporfin (HMME) and talaporfin sodium.[14] For red PWS, colorimetric assessment showed that blanching rates of PDL and PDT at 2 months ranged from 11% to 24% and 22% to 55%, respectively. For purple PWS, PDL and PDT blanching rates ranged from 8% to 33% and 30% to 45%, respectively. Research by K. Gao has shown that PDT is comparably in efficacy to PDL and in some cases may be superior in efficacy.[15] The combination of PDT and PDL provides a synergistic effect that reduces complications to achieve durable vascular occlusion.[16] In recent years, PDT has started to emerge as a new strategy for treating the disease.

Hemoporfin, a second generation photosensitizer consisting of a mixture of two positional isomers of 7(12)-(1-methoxyethyl)-12(7)-(1-hydroxyethyl)-3,8,13,17-tetramethyl-21H,23H-porphyrin-2,18-dipropionic acid, offers advantages such as a stable structure, high singlet oxygen yield, enhanced photoactivity, low dark toxicity and rapid clearance rate.[17] The quantum yield of singlet oxygen ($^1O2$) for HMME is approximately 0.6.[18] Similar to other haematoporphyrin-based PDT photosensitizers, haemoporfin exhibits a prominent Soret band peak and four Q-band peaks at 490 and 630 nm.[19] Following intravenous injection, HMME rapidly reaches peak concentration in the blood and is preferentially taken up by vascular endothelial cells with minimal absorption by epidermal cells. Specific wavelengths of light penetrate the superficial layer and facilitate selective absorption of HMME by vascular endothelial cells. This absorption triggers the generation of singlet oxygen, reactive oxygen species (ROS) and other phototoxic substances that induce apoptosis, necrosis and autophagy of abnormal vascular endothelial cells, while sparing the normal epidermal layer, which is free of HMME and inaccessible normal dermal tissues. This process spares the normal epidermal layer lacking HMME and normal dermal tissue beyond the reach of the laser.[6,20]

In this trial, we treated 33 cases of PWS with HMME-PDT. The overall response rate after HMME-PDT was 90.90%. We observed different therapeutic effects resulting from different types of PWS. Patients with pink-type PWS had higher cure and efficacy rates compared to those with nodular thickening type PWS ($p<0.05$). This finding is consistent with other study studies.[6] Increasing the number of treatments significantly improved the clinical therapeutic effect ($p<0.05$). Patients who received more than three treatments had higher cure and efficacy rates compared to those who received one or two treatments. In addition, patients with purple and nodular thickening type PWS, which are difficult to treat, achieved better therapeutic efficacy with more than three sessions ($p<0.05$). Our study suggests an association between patient age and type of PWS ($p<0.05$). Better efficacy is achieved with initial treatment of pink type PWS, which is predominantly observed at a younger age. Furthermore, increasing age was significantly associated with hypertrophy, consistent with previous research.[21] We observed no significant difference in efficacy between minors and adults patients ($p=0.296$).

Discrepancies with previous study may be due to differences in patient types and treatment frequency between the juvenile and adult cohorts. In particular, purple and nodular thickening types are more common in adult patients, leading to a higher frequency of treatments. Tailored treatment is essential as therapeutic outcome depends on factors such as patient body type, PWS type and treatment frequency. We observed no significant difference in efficacy between patients with PWS lesions in different locations ($p=0.244$). The inconsistent results with previous studies may be due to the insufficient sample size. To date, the evaluation of treatment efficacy for PWS has relied predominantly on subjective assessment by clinicians, as detecting subtle changes can sometimes be challenging. Histopathology, although considered the gold standard, is invasive and difficult to process.[22] CDFI is widely available and offers a non-invasive method of assessing bloodstream signals, providing valuable data.[23] Our study showed that CDFI blood flow analysis revealed significant reductions in blood flow width, blood flow grade and skin thickness after HMME-PDT, indicating vascular

atrophy. CDFI can effectively demonstrate the effect of HMME-PDT on blood vessels. Thus, CDFI appears to be a non-invasive, objective and convenient method to assess the efficacy of HMME-PDT before and after treatment.

After treatment, the main adverse effects of HMME-PDT were pain and oedema, which were alleviated after treatment. Cold sprays or wet compresses could also relieve noticeable symptoms for three to five days. Patients should protect any crusts that form to prevent infection, scarring, pigmentation and hypopigmentation. Following HMME-PDT, patients should avoid sun exposure for two weeks to prevent erythema, pruritus and other allergic reactions. HMME has lower toxicity and shorter term skin phototoxicity, therefore no overt systemic adverse reactions have been observed. After two months, further treatment can be given.

HMME-PDT is generally considered safe for the treatment of nevus erythematosus, with studies showing that both fast- and slow-dosing regimens are effective and safe in treating Chinese children with this condition.[7,20] However, adverse reactions may still occur during treatment. Contraindications may vary depending on the clinical scenario. Contraindications include hypersensitivity or allergic reaction to the drug, pregnancy, lactation, and caution is advised in patients with severe hepatic impairment. Extensive research data on the effects of HMME on the kidneys is lacking, and its safety remains unclear.

Conclusions

In conclusion, HMME-PDT appears to be a promising therapeutic approach for PWS, and CDFI examination serves as a valuable technique for assessing efficacy. However, these conclusions need to be confirmed by randomized controlled trials with a substantial number of cases.

Data Sharing Statement

The data used to support the results of this study are available on request from the corresponding author.

Ethics and Consent Statements

The study was conducted in accordance with the Declaration of Helsinki, and was approved by the Research Ethics Committee of the Third Affiliated Hospital of Soochow University (2017-045). All patients and/or their legal guardians were informed about the purpose of the study, the treatment method, etc., and signed the informed consent form. And the patients and/or their legal guardian(s) gave their permission for the images to be published.

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Disclosure

The authors have no competing interest for this work.

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