Dermatol Ther (Heidelb) (2022) 12:861–869
https://doi.org/10.1007/s13555-022-00699-w

ORIGINAL RESEARCH

The Efficacy of Hematoporphyrin Monomethyl Ether Photodynamic Therapy in Adult Patients with Port-Wine Stains: A Retrospective Study

Xin-yu Zhang · Najwa Al-Odaini · Run-ge Fan · Hong-di Xiong · Jia-can Huang · Hong-mei Dai · Yan-hua Zhou · Xiu-yin Huang · Si-jian Wen

Received: December 10, 2021 / Accepted: February 16, 2022 / Published online: March 4, 2022

ABSTRACT

Introduction: Hematoporphyrin monomethyl ether-photodynamic therapy (HMME-PDT) has been showing promising results in the treatment of port-wine stains (PWSs). We evaluated the clinical efficacy and treatment response of HMME-PDT in adult Chinese patients with PWSs.

Methods: A single-center retrospective study recruited adult PWS patients with negative HMME skin test results from December 2017 to May 2020. Patients received an intravenous injection of 5 mg/kg HMME and the lesions were exposed to 532 nm LED green light with an irradiation power density of 85–95 mW/cm^2 for 20–25 min. Digital photographs were taken before and after two therapy sessions and observed by three blinded dermatologists for clinical response.

Results: A total of 72 patients aged between 18 and 55 years were recruited. There were 65 patients of the flat purple type, 5 of the hypertrophic type, and 2 of the nodular thickening type. Of the 65 patients, 7 showed excellent efficacy (10.77%), 13 patients indicated good efficacy (20.00%), 47 patients showed fair efficacy (64.62%), while 3 cases displayed no improvement (4.62%). All five patients of the purple and hypertrophic type showed fair efficacy (100%), and no improvement was observed in patients of the nodular thickening type (100%). Pain, pruritus, and a burning sensation were observed during treatment. Edema was noted on the treated areas post-treatment. No other obvious systemic adverse reactions were observed.

Conclusion: HMME-PDT is an effective and safe treatment for adult patients with purple PWSs. Multiple HMME-PDT treatments can improve the response and cure rate.

Keywords: Hematoporphyrin monomethyl ether; Photodynamic therapy; Port-wine stain; Adult Chinese patients

X. Zhang · N. Al-Odaini · R. Fan · H. Xiong · J. Huang · H. Dai · Y. Zhou · X. Huang · S. Wen (✉)
Department of Dermatology and Venereology, The First Affiliated Hospital of Guangxi Medical University, Nanning 530021, China
e-mail: wensijian1018@163.com

Key Summary Points
Why carry out this study?
Port-wine stains (PWSs) can have a significant impact on patients and their families, especially when they are associated with disfigurement and hypertrophy.
We assessed the efficacy and safety of Hematoporphyrin monomethyl ether-photodynamic therapy (HMME-PDT) in adult patients in order to provide additional evidence on PWSs treatment options other than traditional methods.
What was learned from the study?
HMME-PDT is an effective and safe treatment for adult patients with PWSs, particularly the purple type.
Multiple HMME-PDT treatments might improve the response and cure rate.

INTRODUCTION

PWSs are congenital low-flow vascular malformations of the skin. Unlike hemangiomas, PWSs do not involute over time, but often continue to progress and evolve into adulthood [1]. At birth, PWSs are typically present as pink-to-red macules or patches; however, they often tend to darken in color with age [2, 3]. Two thirds of the affected individuals develop soft-tissue overgrowth and nodule formation, resulting in disfigurement, asymmetry, and spontaneous bleeding, which creates a tremendous emotional and physical struggle for patients and their families [1, 4–6]. In the past, PWSs were treated with surgery, cryotherapy, dermabrasion, isotope therapy, or copper vapor laser with minimal success, in addition to scar formation, and therefore are not widely applied [7]. Although pulsed dye laser therapy (PDL) is considered the gold standard treatment for PWSs, the cure rate is as low as 6%, and up to 30% of patients do not respond to the therapy [8]. Photodynamic therapy (PDT) is a photochemical interaction-based therapy that has recently become a treatment option for PWSs [9]. These photochemical interactions between light, photosensitizer, and oxygen result in the production of highly reactive oxygen-derived free radicals which cause capillary wall damage and vessel closures [10, 11]. Photocarcinorin is a first-generation photosensitizer that has been used to treat PWSs in combination with a light source; however, it has been associated with prolonged photosensitivity and scar formation [12]. Hematoporphyrin monomethyl ether (HMME, hemoporfin) is a novel porphyrin-related photosensitizer first developed in China that consists of two positional isomers of 7(12)-(1-methoxyethyl)-12(7)-(1-hydroxyethyl)-3,8,13,17-tetramethyl-21H,23H-porphin-2,18-di-propionic acid and is clinically preferred over photocarcinorin due to its shorter photosensitivity period (2 weeks) [12, 13]. A previous retrospective study suggested that PDT is as effective as 585 nm PDL for pink PWSs in pediatric patients [14]. Another study suggested that HMME-PDT is an effective and safe treatment for pediatric patients with PWSs [9]. However, HMME-PDT effectiveness in adult patients with PWSs still needs further studies. Hence, we performed the current study to evaluate the efficacy and safety of HMME-PDT in treating adult patients with PWS.

METHODS

Study and Patients

A retrospective single-center study was conducted at the Dermatology Department of Guangxi Medical University First Affiliated Hospital, Nanning, China from December 2017 to May 2020. Inclusion criteria were: adults with normal renal and hepatic functions and no previous therapy for PWS with laser, PDT, isotope, topical, or systemic treatment in the last 4 weeks. The exclusion criteria were: known allergy to HMME or its chemical ingredients, scar diathesis, severe hepatic or renal insufficiency. This study was approved by the Ethics

Committee of the First Affiliated Hospital of Guangxi Medical University. Written informed consent was obtained from all participants prior to enrollment. The demographic data of patients was collected and analyzed. Lesion color was determined based on photographs taken before treatment, and the type was identified based on clinical examination of the lesion. All patients were treated twice at 2-month intervals.

Preparations

Hemoporfin powder was obtained from Shanghai Fudan-Zhangjiang Bio-Pharmaceutical Co Ltd. All patients received skin tests as previously mentioned [15]. In brief, HMME was diluted in 10 ml of normal saline and 0.1 ml of solution (containing 10 mg HMME) was further diluted with 8 ml of normal saline to a final concentration of 125 μg/ml. Then, 0.1 ml diluent was injected into the inner side of one forearm, and normal saline was injected into the opposite side for a blank control test. A skin test reaction was observed 20 min later. Digital photographs of the lesions were collected and the photosensitizer dosage was calculated (5 mg/kg). The surrounding normal skin was covered with multiple layers of black fabric. No local anesthetics were used prior to the sessions and all patients wore protective goggles.

Intervention

Patients received a slow injection of photosensitizer via a venous pump for 10 min, the channel was then flushed with normal saline to ensure its entrance into the blood circulation. Immediately after injection, the treated area was fully exposed in a horizontal plane to a 532 nm LED green light (LED-IE, Wuhan YaGe Photoelectric Technology Co., Ltd) with a power density of 85–95 mW/cm^2 for 20–25 min.

Post-Treatment Care

Ice-cold compressions were used to reduce pain and cool the skin. Mild topical corticosteroid cream (desonide) was prescribed for 3–7 days post treatment. Patients were advised to avoid strong light and sunshine, apply sunscreen, wear a hat, sunglasses, and cover up for at least 14 days post treatment.

Clinical Efficacy Evaluation

Digital photographs before and after treatment were taken using the same light source. In addition, standardized digital photos using VISIA skin imaging were taken. After two treatment sessions, three blinded dermatologists (not participating in the study) independently reviewed the photos. Efficacy evaluation standards: excellent efficacy, the color nearly or completely resolved in the treated area ($\geq$ 90% improvement); good efficacy, the color significantly faded in the treated area ($\geq$ 60 to $<$ 90% improvement); fair, the color partially faded in the treated area ($\geq$ 20 to $<$ 60% improvement); no improvement, the color was mostly unchanged in the treated area ($<$ 20% improvement) [16].

Follow-Up

Follow-up was conducted through an online group chat where patients could immediately report post-session reactions such as edema, crusts, or discolorations in the treated areas. Patients were scheduled for visits every 3 months to evaluate their renal and liver function.

Statistical Methods

Data were analyzed using SPSS 22.0 statistical software. For the comparison of response rates across groups, the χ^2 and Fisher's exact tests were used. $p < 0.05$ was considered statistically significant.

RESULTS

Patients

A total of 72 adult Chinese patients with Fitzpatrick phototype III-IV were enrolled in the study. The average age was 24.36 (18–55 years)

and 38.89% were males (28/72). None of the participating patients had received any form of treatment before the HMME-PDT treatment. Lesions were mainly located on the face (58 patients), followed by the forearm and fingers in 8 patients, neck in 4 patients, and extremities in 2 patients. In the majority of participating patients, the size of the skin lesions was within 0–10 cm (65 patients). Lesions were mainly of the purple flat type (65 patients), 5 of the purple hypertrophic type, and 2 of the nodular thickening type (Table 1).

Efficacy

After two HMME-PDT sessions, in the purple flat type group, excellent efficacy was observed in 7 patients (10.77%); good efficacy in 13 patients (20.00%); fair in 47 patients (64.62%), and no improvement in 3 (4.62%). All five patients with the purple and hypertrophic type showed fair efficacy (100%), and no efficacy was observed in patients with nodular thickening type (100%) (Fig. 1).

There were no differences in excellent and good efficacy response rates between male and female patients ($p = 0.604$), nor with their lesions' size ($p = 0.546$). The excellent and good efficacy response rates in patients aged 20–-30 years were higher than those in other age groups, it was the highest in patients with lesions located on the face and neck as compared to lesions on the extremities ($p < 0.05$), and higher in patients of the purple flat type than those of the purple and hypertrophic types ($p < 0.05$) (Table 2).

Table 1 Demographic data ($n = 72$)

Characteristics	Value
Female, *n* (%)	44 (61.11)
Male, *n* (%)	28 (38.89)
Location of PWS	
Face	58 (80.56)
Neck	4 (5.56)
Extremities	10 (13.88)
Type of PWS	
Purple flat type	65 (90.28)
Purple type with hypertrophy	5 (6.94)
Nodular thickening type	2 (2.78)
Age at initiation of therapy	
18–20	25 (34.72)
20–30	37 (51.39)
30–40	7 (9.72)
40–50	2 (2.78)
50–60	1 (1.39)

Adverse Effects

During treatment, all participants showed variable degrees of burning sensation and pain; two patients of the nodular thickening type could not continue the session due to severe pain. Consequently, general anesthesia was used in the next session. A variable degree of pruritus was shown by 66 patients. Those who experienced intensive pruritus were able to continue the treatment after cold spraying.

Follow-Up

Patients are being followed-up to date ($\geq$ 1 year). All patients showed variable degrees of edema; purpura in the treated area was observed in 36 patients; crusting was observed in 11 patients, and 1 patient showed urticaria (Fig. 2). No other obvious systemic adverse reactions were observed. The majority of adverse reactions subsided within 2 weeks with general management. Patients' liver and kidney function remained within normal values during the period of follow-up.

Recurrence was seen in three patients with flat purple type; one patient ($\sim$ 14.3%) from the excellent efficacy group 6 months after the session and two patients ($\sim$ 15.4%) from the good efficacy group 5–8 months after the session.

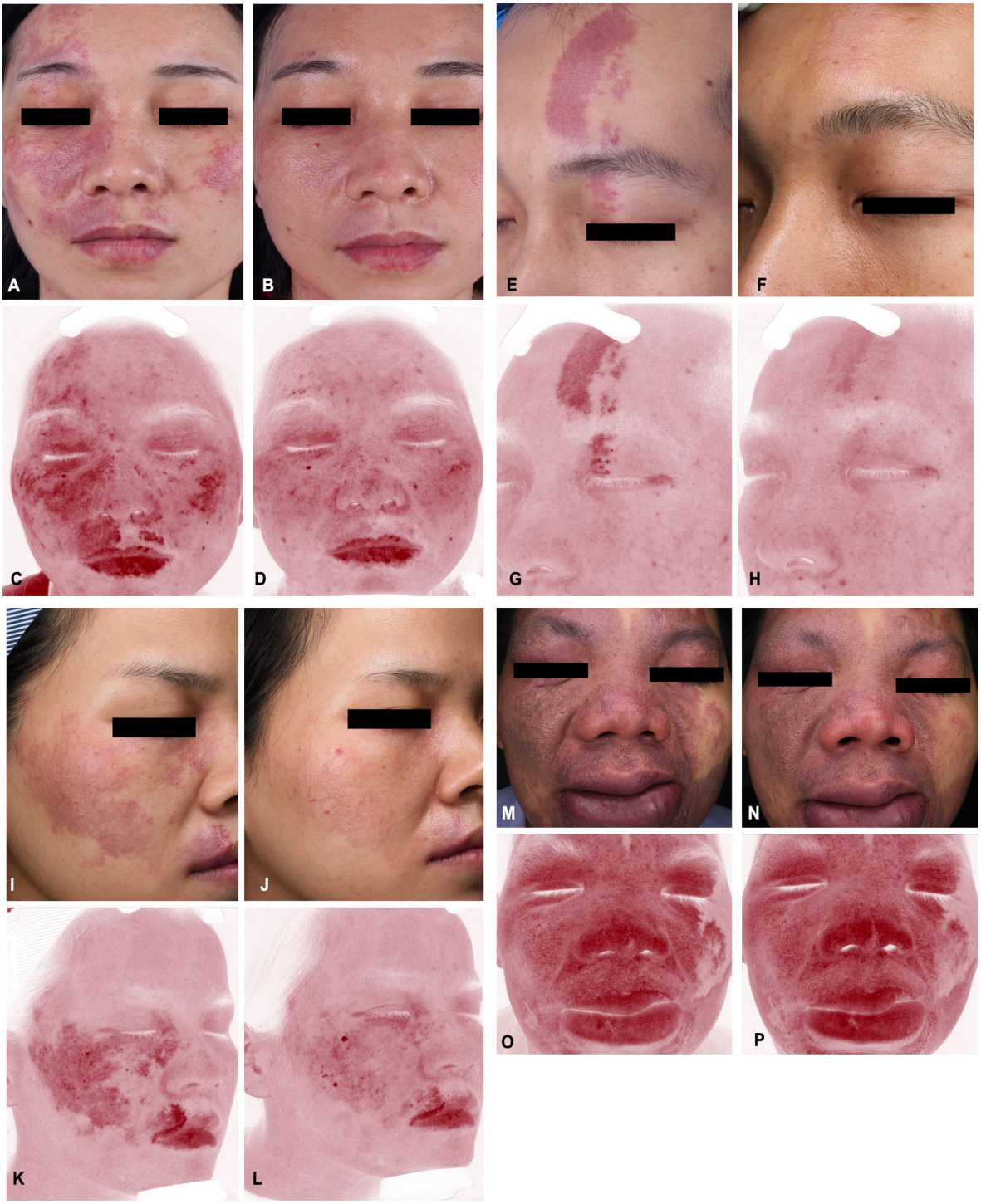

Fig. 1 PWSs before and after two HMME-PDT sessions. **A–D** excellent efficacy; **E–H** good efficacy in a case with purple flat type; **I–L** fair efficacy in a case with purple flat type; **M–P** no improvement in a case with nodular thickening type

Table 2 Different characteristics of PWS and efficacy

Variables	Cases	Excellent, *n* (%)	Good, *n* (%)	Fair, *n* (%)	No improvement, *n* (%)	*P* value
Gender						0.604
Female	44	6 (13.64)	6 (13.64)	30 (68.18)	2 (4.54)	
Male	28	1 (3.57)	7 (25.00)	17 (60.71)	3 (10.71)	
Age						0.040
18–20	25	1 (4.00)	1 (4.00)	23 (88.00)	0	
20–30	37	4 (10.81)	9 (24.32)	21 (56.76)	3 (8.11)	
30–40	7	2 (28.57)	3 (42.86)	1 (14.29)	1 (14.29)	
40–50	2	0	0	2 (100%)	0	
50–60	1	0	0	0	1 (100)	
Type						0.014
Purple flat	65	7 (10.77)	13 (20.00)	42 (64.62)	3 (4.62)	
Purple + hypertrophy	5	0	0	5 (100)	0	
Nodular thickening type	2	0	0	0	2 (100)	
Location of PWS						0.000
Face	58	6 (10.34)	10 (17.24)	40 (68.97)	2 (3.45)	
Arm or leg	10	0	0	7 (70.00)	3 (30.00)	
Neck	4	1 (25.00)	3 (75.00)	0	0	
Size						0.546
< 5 cm $\times$ 5 cm	30	4 (13.33)	5 (16.67)	19 (63.33)	2 (6.67)	
≥ 5 cm $\times$ 5 cm $<$ 10 cm $\times$ 10 cm	35	3 (8.57)	7 (20.00)	23 (65.71)	2 (5.71)	
≥ 10 cm $\times$ 10 cm	7	0	1 (14.29)	5 (71.29)	1 (14.29)	
Recurrence						1.000
Purple flat	65	1/7 (14.29)	2/15 (13.33)	0	0	
Purple + hypertrophy	5	0	0	0	0	
Nodular thickening type	2	0	0	0	0	

DISCUSSION

We performed a retrospective analysis of 72 patients to investigate the efficacy of HMME-PDT in the treatment of PWS in adult Chinese patients with skin type III–IV. The results of our research showed that HMME-PDT is an effective and safe treatment for adult individuals with PWS, particularly the purple type.

Previous studies have shown that regardless of the lesion site, size, or type, the total effective rate of HMME-PDT treatment of PWSs in different age groups can be as high as 97.78% and 99.75% [17, 18].

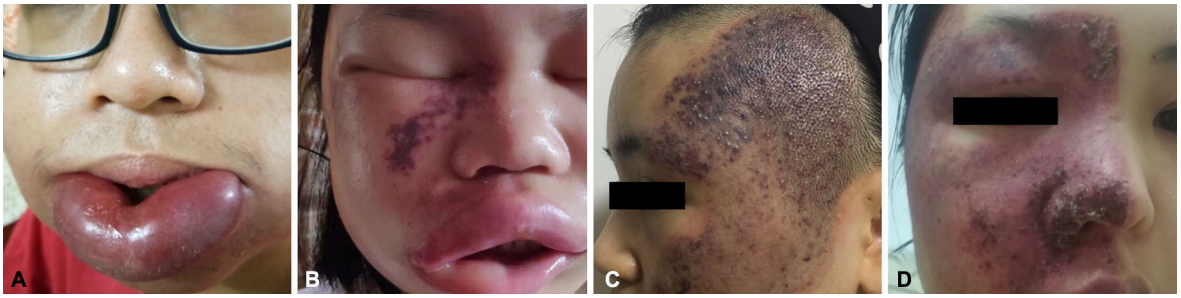

Fig. 2 Post-treatment adverse effects: **A**, **B** intensive edema; **C** purpura; **D** crusting and purpura

Li-qiang et al. used HMME-PDT therapy to treat PWS in Chinese pediatric patients: 29.27% of patients showed an excellent efficacy (cured) after two HMME-PDT treatments, 41.46% showed good efficacy, and 19.51% showed alleviation (fair) where most of the patients were of the pink type [9]. Unlike the pediatric study, the majority of lesions in our study were of the purple flat type, and we gained an overall lower rate of excellent and good efficacy (10.77% and 20.00%, respectively). Yuan et al. achieved higher excellent and good efficacy (37.0%, 94.2%, respectively) treating adult patients with HMME-PDT; however, a copper vapor laser was used and the sample size was larger than the current study [14].

After two HMME-PDT sessions, we observed an overall higher response rate compared with $\geq$ 3 sessions of PDL in lesions from similar age groups and skin types reported in a previous study [19]. Irrespective of the small sample size, K. Gao et al. [20] reported a lower improvement response (fair) in a side-by-side comparison of PDL and PDT treatment of purple flat PWS lesions in adults (8–33% and 30–45%, respectively), demonstrating that PDT is at least as effective as and, in some cases, superior to PDL. In fact, Y. Han et al. recently reported that HMME-PDT is an alternative option for treating PDL-resistant PWSs [21]. In this study, compared with Gao et al. [20], we achieved better responses from a similar age group and lesion type (10.77% excellent, 20.00% good, and 64.62% fair).

According to our findings, patients with lesions on the face or neck had better efficacy rates than patients with lesions on the extremities. Gan et al. had similar findings and hypothesized that lesions located in thinner skin areas have easier irradiation penetration [9]. In this study, patients aged 20–30 years old showed better efficacy than those in other age groups. Furthermore, we found no correlation between the size of the skin lesion and the efficacy of the treatment.

The adverse effects observed during treatment included a burning sensation and pain, which could subside after applying a cold spray or treatment suspension. Local adverse effects after treatment included edema, which could be relieved with ice compression and greatly subsided within 7 days. Purpura usually resolved within 21 days, itching was relieved with oral antihistamines, and crusting would spontaneously fade 2 months later. Interestingly, none of the patients had post-treatment scar formation, and we have not observed any other systemic adverse reactions to date. It should be noted that the treatment needs strict post-treatment care, which might be easier to achieve with adult patients.

Recurrence was observed in three patients several months after treatment, where they received additional (1 $\sim$ 2) sessions and have observed no recurrence to date. In our experience, multiple HMME-PDT treatments can improve the response rate.

The main limitations in our study were the small numbers of patients in some subgroups and the evaluation depending mainly on visual assessment. Therefore, the use of objective assessment tools such as chromameter and controlled trials with a larger sample size is needed to help investigate the real value of

HMME-PDT and to further analyze the relationship between age, type, location, frequency, and number of therapy sessions in adult patients with PWS.

CONCLUSION

The current study demonstrates that HMME-PDT is an effective and safe treatment for PWS in adult patients, especially the purple type. Recurrence is possible; therefore, additional HMME-PDT sessions might be required for better efficacy in persistent PWS lesions.

ACKNOWLEDGEMENTS

The authors would like to thank the patients and their families for allowing us to share their photographs. We are grateful to all the staff at Dermatology and Venerology Surgery room of The First Affiliated Hospital of Guangxi Medical University for their invaluable assistance during procedures.

Funding. This study was supported by grants from the Health Commission of Guangxi Autonomous Region of China (Z20201258) and (2020GXNSFAA297150). No funding or sponsorship was received for the publication of this article. The Journal's Rapid Service Fee was funded by the authors.

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

Author Contributions. Xin-yu ZHANG and Si-jian WEN designed and supervised the study. Xin-yu ZHANG, Najwa AL-ODAINI, Run-ge FAN, Hong-di XIONG, Jia-can HUANG, Hong-mei DAI, Yan-hua ZHOU, Xiu-yin HUANG and Si-jian WEN participated in the treatment process and procedures. Xin-yu ZHANG, Najwa AL-ODAINI and Si-jian WEN wrote the manuscript. All authors have provided final approval of the manuscript.

Disclosures. Xin-yu ZHANG, Najwa AL-ODAINI, Run-ge FAN, Hong-di XIONG, Jia-can HUANG, Hong-mei DAI, Yan-hua ZHOU, Xiu-yin HUANG and Si-jian WEN all have nothing to disclose.

Compliance with Ethics Guidelines. This study was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University. This study was performed in accordance with the Helsinki Declaration. Informed consent was obtained from all participants for possible publications of their digital photographs.

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

REFERENCES

1. Minkis K, Geronemus R, Hale EK. Port wine stain progression: a potential consequence of delayed and inadequate treatment? Lasers Surg Med. 2009;41(6):423–6.

2. van Drooge AM, Beek J, van der Veen JP, van der Horst CM, Wolkerstorfer A. Hypertrophy in port-wine stains: prevalence and patient characteristics in a large patient cohort. J Am Acad Dermatol. 2012;67:1214–9.

3. Geronemus RG, Ashinoff RL. The medical necessity of evaluation and treatment of port-wine stains. J Dermatol Surg Onco. 1991;17(1):76–9.

4. Malm M, Carlberg M. Port-wine stain—a surgical and psychological problem. Ann Plast Surg. 1988;20:512–6.

5. Miller AC, Pit-Ten CI, Watson HS, Geronemus RG. Stress and family satisfaction in parents of children with facial portwine stains. Pediatr Dermatol. 1999;16:190–7.

6. Enjolras O, Riché M. Port-wine stains. Arch Dermatol. 1985;121(7):834.

7. Wang Y, Huang Z, Yuan K. Current treatment and study advance of photodynamic therapy in treatment of PWS. J Pract Dermatol. 2015;8(5):363–70.

8. Wu Q, Tu P, Zhou G, Yang H, Zhou Z, Zhao Y, Zheng Q, Gu Y, Tao J, Zhu X. A dose-finding study for hemoporfin in photodynamic therapy for port-wine stain: a multicenter randomized double-blind phase IIb trial. Photodermatol Photoimmunol Photomed. 2018;34(5):314–21.

9. Gan L-Q, Wang H, Ni S-L, Tan C-H. A clinical study of HMME-PDT therapy in Chinese pediatric patients with port-wine stain. Photodiagn Photodyn Ther. 2018;23:102–5.

10. Jiang L, Gu Y, Li X, Zhao X, Li J, Wang K, Liang J, Pan Y, Zhang Y. Changes of skin perfusion after photodynamic therapy for port wine stain. Chin Med J (Engl). 1998;111(2):136–8.

11. Zhao Y, Zhou Z, Zhou G, Tu P, Zheng Q, Tao J, et al. Efficacy and safety of hemoporfin in photodynamic therapy for port-wine stain: a multicenter and open-labeled phase IIa study. Photodermatol Photoimmunol Photomed. 2011;27:17–23.

12. Ma G, Han Y, Ying H, Zhang X, Yu W, Zhu J, Cen Q, Chen H, Jin Y, Lin X. Comparison of two generation photosensitizers of psd-007 and hematoporphyrin monomethyl ether photodynamic therapy for treatment of port-wine stain: a retrospective study. Photobiomodul Photomed Laser Surg. 2019;37(6):376–80.

13. Huang Z. An update on the regulatory status of PDT photosensitizers in China. Photodiagnosis Photodyn Ther. 2008;5:285–7.

14. Yuan KH, Li Q, Yu WL, Zeng D, Zhang C, Huang Z. Comparison of photodynamic therapy and pulsed dye laser in patients with port wine stain birthmarks: a retrospective analysis. Photodiagn Photodyn Ther. 2008;5:50–7.

15. Zhang Y, Zou X, Chen H, et al. Clinical study on clinical operation and post-treatment reactions of HMME-PDT in treatment of PWS. Photodiagn Photodyn Ther. 2017;20:253–6.

16. Zhao Y, Tu P, Zhou G, et al. Hemoporfin photodynamic therapy for portwine stain: a randomized controlled trial. PLoS ONE. 2016;11(5):0156219.

17. Khalaf AT, Sun Y, Wang F, Sheng M, Li Y, Liu X. Photodynamic therapy using HMME for port-wine stains: clinical effectiveness and sonographic appearance. Biomed Res Int. 2020;2020:6030581.

18. Gu Y, Huang N, Liang J, Pan YM, Liu FG. Clinical study of 1949 cases of port wine stains treated with vascular photodynamic therapy (Gu's PDT). Ann Dermatol Venereol. 2007;134:241–4.

19. Shi W, Wang J, Lin Y, Geng J, Wang H, Gong Y, Liu H, Zhang F. Treatment of port wine stains with pulsed dye laser: a retrospective study of 848 cases in Shandong Province, People's Republic of China. Drug Des Dev Ther. 2014;8:2531–8.

20. Gao K, Huang Z, Yuan KH, Zhang B, Hu ZQ. Side-by-side comparison of photodynamic therapy and pulsed-dye laser treatment of port-wine stain birthmarks. Br J Dermatol. 2013;168(5):1040–6.

21. Han Y, Ying H, Zhang X, Yu W, Cen Q, Chen X, Qiu Y, Chen H, Jin Y, Ma G, Lin X. Retrospective study of photodynamic therapy for pulsed dye laser-resistant port-wine stains. J Dermatol. 2020;47(4):348–55.