Efficacy of hemoporfin photodynamic therapy for pulsed dye laser-resistant facial port-wine stains in 107 children: A retrospective study

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Abstract

Background: Port-wine stains occur in 0.3–0.5% newborns, mainly on the face and neck. Pulsed dye laser is recognized as the gold standard treatment; nevertheless, it is associated with a low cure rate and a high recurrence rate.

Aims: This study aims to evaluate the efficacy of hemoporfin photodynamic therapy for pulsed dye laser-resistant port-wine stains in children.

Methods: We studied 107 children who received hemoporfin photodynamic therapy for port-wine stains on the face and neck that were resistant to pulsed dye laser. After intravenous injection of 5 mg/kg hemoporfin, the local lesion was irradiated with 532 nm LED green light for 20 min with a power density of 80–100 mW/cm^2. A total of 65 patients were given a second treatment after eight weeks. The efficacy and therapeutic responses were recorded at four days and eight weeks after each treatment.

Results: The efficacy was positively correlated with the number of treatments received; two treatment sessions yielded significantly better results compared to a single treatment with a response rate of 96.9%, a significant response rate of 50.8% and a cure rate of 21.5%, respectively ($P < 0.001$). After two treatment sessions, the efficacy was negatively correlated with age ($P = 0.04$). The efficacy for port-wine stains located on the lateral part was better than that of the central face ($P = 0.04$). The efficacy for the pink type was better than that for the red and purple types ($P = 0.03$). No allergic or systematic adverse reactions were reported.

Limitations: No objective measurement data were available.

Conclusion: Hemoporfin photodynamic therapy is effective and safe for pulsed dye laser-resistant facial port-wine stains in children.

Key words: Children, facial port-wine stains, hemoporfin photodynamic therapy, pulsed dye laser resistant

Plain Language Summary

We studied 107 children who received hemoporfin photodynamic therapy for port-wine stains on the face and neck that were resistant to pulsed dye laser. We found it effective and safe. Two treatment sessions yielded better results compared to a single treatment with a response rate of 96.9%, a significant response rate of 50.8% and a cure rate of 21.5%, respectively. Younger children responded better. The efficacy for port-wine stains of the lateral part was better than that of the central face. The efficacy for the pink type was better than that for the red and purple types. No allergic or systematic adverse reactions were reported.

Introduction

Port-wine stains are common congenital dermal capillary malformations of the skin with a reported incidence of 0.3–0.5% in newborns and approximately 95% occurring on the face and neck.[1] They are classified as pink, red, purple and nodular thickening types.[2] As the patient ages, port-wine stains gradually worsen, and nodules or ruptures may appear. Therefore, they are recommended to be treated at an

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early age. Pulsed dye laser is recognized as the gold standard therapy based on the theory of selective photothermolysis. Nevertheless, fewer than 10% of lesions achieve complete clearance, and 20–30% respond poorly with recurrence occurring in nearly 50%.[3] Vascular targeting photodynamic therapy is based on the interactions of light, photosensitizer and oxygen. It is more efficient and requires fewer treatment sessions than pulsed dye laser. It acts on target vessels with a diameter of 10–50 μm that respond poorly to pulsed dye laser.[4] Hematoporphyrin monomethyl ether is the new generation of photosensitizer. Compared with the first generation of photosensitizer, it is associated with better safety and requires shorter periods of sunlight avoidance (two weeks) and treatment intervals. It is also highly reliable in children.[1,5] Our department used it in 107 cases of children with port-wine stains on the face and neck and achieved good results.

Methods

After Institutional Review Board approval (KS202056), the data of 107 children diagnosed with port-wine stains on the face and neck (from 2018 to 2019) who were treated with hematoporphyrin monomethyl ether photodynamic therapy were obtained in the department of dermatology in Wuxi People's Hospital. All patients had previously been treated with at least five sessions of pulsed dye laser and had not improved for at least the last two consecutive treatments.

Hematoporphyrin monomethyl ether, the trade name hemoporfin, was produced by Shanghai Fudan-Zhangjiang Bio-Pharmaceutical Co., Ltd. It was administered at five mg/kg. Under the condition of avoiding strong light, an infusion pump was used to inject the drug at a constant speed over 20 min intravenously. For children who were one–three years old, sedation with chloral hydrate was used. Lesions were then exposed to 532 nm LED green light (Wuhan YaGe LED1 modified machine, Wuhan YaGe Photoelectric Technology Co., Ltd.) five–ten minutes after drug administration and lasted for 20 min with the irradiation power density of 80–100 mW/cm^2 and energy density of 90–190 J/cm^2. The light beam was kept perpendicular to the irradiation plane. The interval between two treatments was eight weeks. It was advised to avoid strong light within two weeks after each treatment. An ice bag was required for the first 48 h after treatment. Safety and efficacy were evaluated during outpatient follow-up at four days and eight weeks after each treatment. Before each treatment, three examinations were performed: (1) digital photographs under a fixed light source; (2) VISIA scan images with VISIA-CR™ system (Canfield Imaging Systems, USA); and (3) dermoscopy images of the same area with ×20 polarized light (DMT-200, Beijing Dermat Speedy Recovery T&D Co., Ltd.). The efficacy was judged by four dermatologists who were not involved in this study. They made the assessment independent of each other. The results were deemed valid only if three or more evaluators agreed; otherwise, the response was reevaluated until a consensus of three or more was achieved. We also recorded adverse reactions, including edema, crust, blister, inflammatory erythema, infection, pigment changes and scar. Complete blood counts, routine urine test, liver and renal function tests and electrocardiograms were performed in all patients before and four days after each treatment.

Clinical efficacy evaluation

After each treatment, efficacy was observed eight weeks later by comparing the clinical, VISIA and dermoscopic images before and after treatment. Efficacy evaluation standards: excellent improvement: the color mostly faded (improvement ≥90%); good improvement: the color significantly faded (improvement ≥60%, <90%); moderate improvement: the color partially faded (improvement ≥20%, <60%) and no improvement: the color was mostly unchanged (improvement < 20%).[6,7] Post-treatment crust thickness: thin crust: thickness <0.5 mm, thick crust: thickness ≥0.5 mm. The patients' parents were asked to rate their satisfaction with each treatment on a Likert satisfaction scale (five, very satisfied; four, satisfied; three, slightly satisfied; two, dissatisfied and one, very dissatisfied).

Statistical analysis

SPSS 22.0 statistical software was used for data analysis. Wilcoxon signed-rank test was conducted to analyze the efficacy of different treatment sessions, and Kruskal–Wallis test was used for the analysis of the efficacy in various age groups, lesion locations and subtypes. $P < 0.05$ was considered statistically significant.

Results

Patient clinic-demographic profile

The patients were aged between one and 14 with the average age of 4.82 years old, including 48 males and 59 females. There were 103 patients with involvement of either the central part or the lateral part of the face, two patients with involvement only on the neck, one patient with facial port-wine stains involving both the lateral and the central part and one patient with involvement of both the lateral part of the face and the neck [Table 1].

Efficacy

A total of 65 of the 107 patients were given a second treatment after eight weeks. The other 42 patients did not receive a second treatment for various personal reasons. We first compared the efficacy between one and two treatment sessions, and then the efficacy in various age groups, lesion locations and subtypes in those who received two treatment sessions [Table 2]. In addition to clinical photographs, we analyzed the red images of VISIA and the vascular changes of the dermoscopy images to further assess the efficacy. VISIA Complexion Analysis System is used to analyze facial skin, which collects images that can be kept in the same light and angle. The red images can also reflect the depth and size of facial erythema. In the "response" group, VISIA images showed that the degree of redness or area size was reduced after treatment, and dermoscopy revealed that the density

and redness of blood vessels were also reduced. Typical post-operative photographs are shown in Figures 1-2.

Comparison of efficacy between one and two treatment sessions

For a single treatment in 107 patients, excellent improvement was achieved in ten (9.3%) cases, good-to-excellent improvement was achieved in 35 (32.7%) cases and moderate-to-excellent improvement was achieved in 95 (88.8%) cases. After two sessions of treatments in 65 patients, 14 (21.5%) achieved excellent improvement, 33 (50.8%) achieved good-to-excellent improvement and 63 (96.9%) achieved moderate-to-excellent improvement. The efficacy of two treatment sessions was better than that of one ($P < 0.001$).

For a single treatment, there were 14 (13.1%) patients' parents who were "very satisfied," 35 (32.7%) were "satisfied," 35 (32.7%) were "slightly satisfied," 22 (20.6%) were "dissatisfied" and one (0.9%) was "very dissatisfied" with a mean score of 3.36 (SD = 0.98). After two treatment sessions, there were 12 (18.5%) patients' parents who were "very satisfied," 30 (46.2%) were "satisfied," 19 (29.2%) were "slightly satisfied," four (6.1%) were "dissatisfied" and none was "very dissatisfied" with a mean score of 3.77 (SD = 0.82) [Table 3].

Table 1: Characteristics of patients (*n*=107)

Characteristics	Number of cases (%)
Sex	
Female	59 (55.1)
Male	48 (44.9)
Age (years)	
1–2	35 (32.7)
3–6	41 (38.3)
7–14	31 (29.0)
Location of port-wine stains	
Central of face	63 (57.8)
Lateral of face	43 (39.4)
Neck	3(2.8)
Subtype of port-wine stains	
Pink type	27 (25.2)
Red type	57 (53.3)
Purple type	23 (21.5)
Nodular thickening type	None
Times of photodynamic therapy	
One time	107 (100)
Two times	65 (60.7)

Comparison of efficacy in various age groups after two treatment sessions

Among the 65 patients, 18 were one–two years old, and in this age group, five (27.8%) achieved excellent improvement after two treatment sessions, 12 (66.7%) achieved good-to-excellent improvement and all (100%) showed moderate-to-excellent improvement. Twenty nine patients were three–six years old, and in this age group, six (20.7%) achieved excellent improvement, 14 (48.3%) achieved good-to-excellent improvement and all (100%) showed moderate-to-excellent improvement. There were 18 patients of seven–14 years old, and in this age group, three (16.7%) achieved excellent improvement, seven (38.9%) achieved good-to-excellent improvement and 16 (88.9%) showed moderate-to-excellent improvement. The difference was statistically significant ($P = 0.04$).

Comparison of efficacy in different anatomical locations after two treatment sessions

Out of 65 patients, 42 had lesions on the central face, and among them, excellent improvement was achieved in five (11.9%), good-to-excellent improvement was achieved in 18 (42.9%) and moderate-to-excellent improvement was

Table 2: Different characteristics of port-wine stains and efficacy

	Case	EI	GI	MI	NI	Cure rate (%)	Significant response rate (%)	Response rate (%)	*P*-value
Number of treatments									
One time	107	10	25	60	12	9.3	32.7	88.8	<0.001
Two times	65	14	19	30	2	21.5	50.8	96.9	
Patients with two treatment sessions									
Age (years)									
1–2	18	5	7	6	0	27.8	66.7	100	0.04
3–6	29	6	8	15	0	20.7	48.3	100	
7–14	18	3	4	9	2	16.7	38.9	88.9	
Location of port-wine stains									
Central of face	42	5	13	22	2	11.9	42.9	95.2	0.04
Lateral of face	22	8	6	8	0	36.4	63.6	100	
Subtype of port-wine stains									
Pink type	15	6	5	4	0	40.0	73.3	100	0.03
Red type	34	6	11	17	0	17.6	50	100	
Purple type	16	2	3	9	2	12.5	31.3	87.5	
Nodular thickening type	0	0	0	0	0	0.0	0.0	0.0	

EI: Excellent improvement, GI: Good improvement, MI: Moderate improvement, NI: No improvement. Cure: Excellent improvement was achieved; Significant response: Good to excellent improvement was achieved; Response: Moderate to excellent improvement was achieved

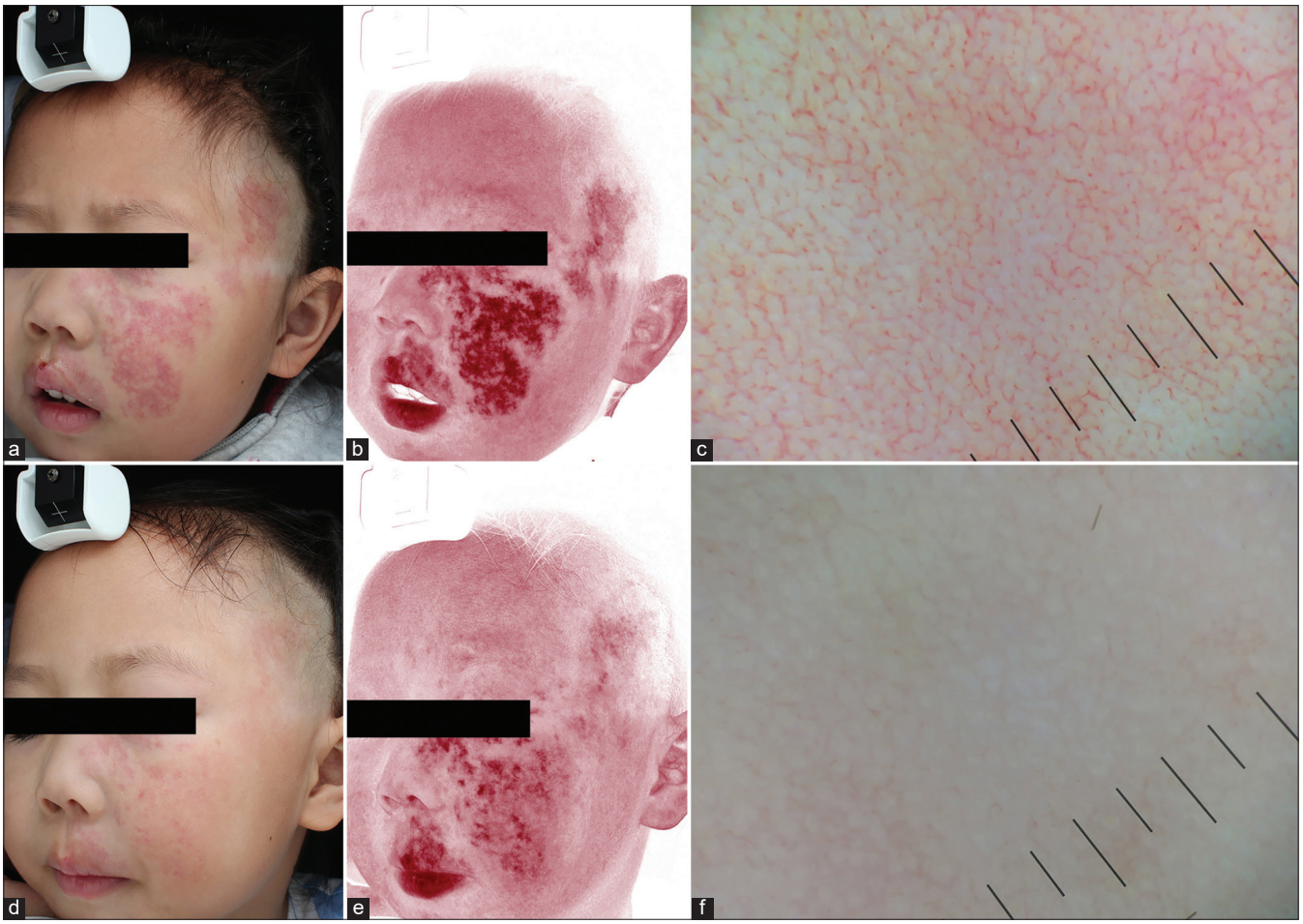

Figure 1: (a) A 6-year-old girl with port wine stains on the left face, (b) a large area of redness appeared in the lesion, (c) many reticular vessels and a few scattered punctate vessels appeared before treatment. (d) the erythema decreased in size and became lighter in color with good improvement after a single treatment, (e) the degree of redness and area size reduced significantly (6500-K standard white light and polarized light source, VISIA), (f) the density and redness of blood vessels reduced significantly after 8 weeks of a single treatment (DMT-200, polarized, ×20)

Table 3: Parents satisfaction

Likert satisfaction scale	Number of patients (%)	
	One session	Two sessions
1 (Very dissatisfied)	1 (0.9)	0 (0)
2 (Dissatisfied)	22 (20.6)	4 (6.1)
3 (Slightly satisfied)	35 (32.7)	19 (29.2)
4 (Satisfied)	35 (32.7)	30 (46.2)
5 (Very satisfied)	14 (13.1)	12 (18.5)
Mean score	3.36 (SD=0.98)	3.77 (SD=0.82)

achieved in 40 (95.2%) cases after two treatment sessions. Among the 22 patients with lesions of the lateral area, eight (36.4%) achieved excellent improvement, 14 (63.6%) achieved good-to-excellent improvement and all (100%) achieved moderate-to-excellent improvement. The difference was statistically significant ($P = 0.04$).

Comparison of efficacy in different subtypes after two treatment sessions

Among the 65 patients, there were 15 of pink type. Six (40.0%) of the cases with this subtype achieved excellent improvement, 11 (73.3%) achieved good-to-excellent improvement and all (100%) achieved moderate-to-excellent improvement after two treatment sessions. In the 34 patients with red type, six (17.6%) achieved excellent improvement, 17 (50%) achieved good-to-excellent improvement and all (100%) achieved moderate-to-excellent improvement. In the 16 patients with purple type, two (12.5%) achieved excellent improvement, five (31.3%) achieved good-to-excellent improvement and 14 (87.5%) achieved moderate-to-excellent improvement. The difference was statistically significant ($P = 0.03$).

Adverse effects after treatment

After treatment, varying degrees of edema appeared in the irradiated area in all patients (100%), reaching a peak within two–three days and completely subsiding within one week. Thirty nine (36.4%) patients experienced crusting, 38 of which were thin and gradually fell off within two weeks. One (0.9%) patient had thick crust that developed to hypertrophic scar which was alleviated during subsequent treatments. Ten (9.3%) patients exhibited mild hyperpigmentation and one (0.9%) exhibited hypopigmentation in the treated area, all of which were

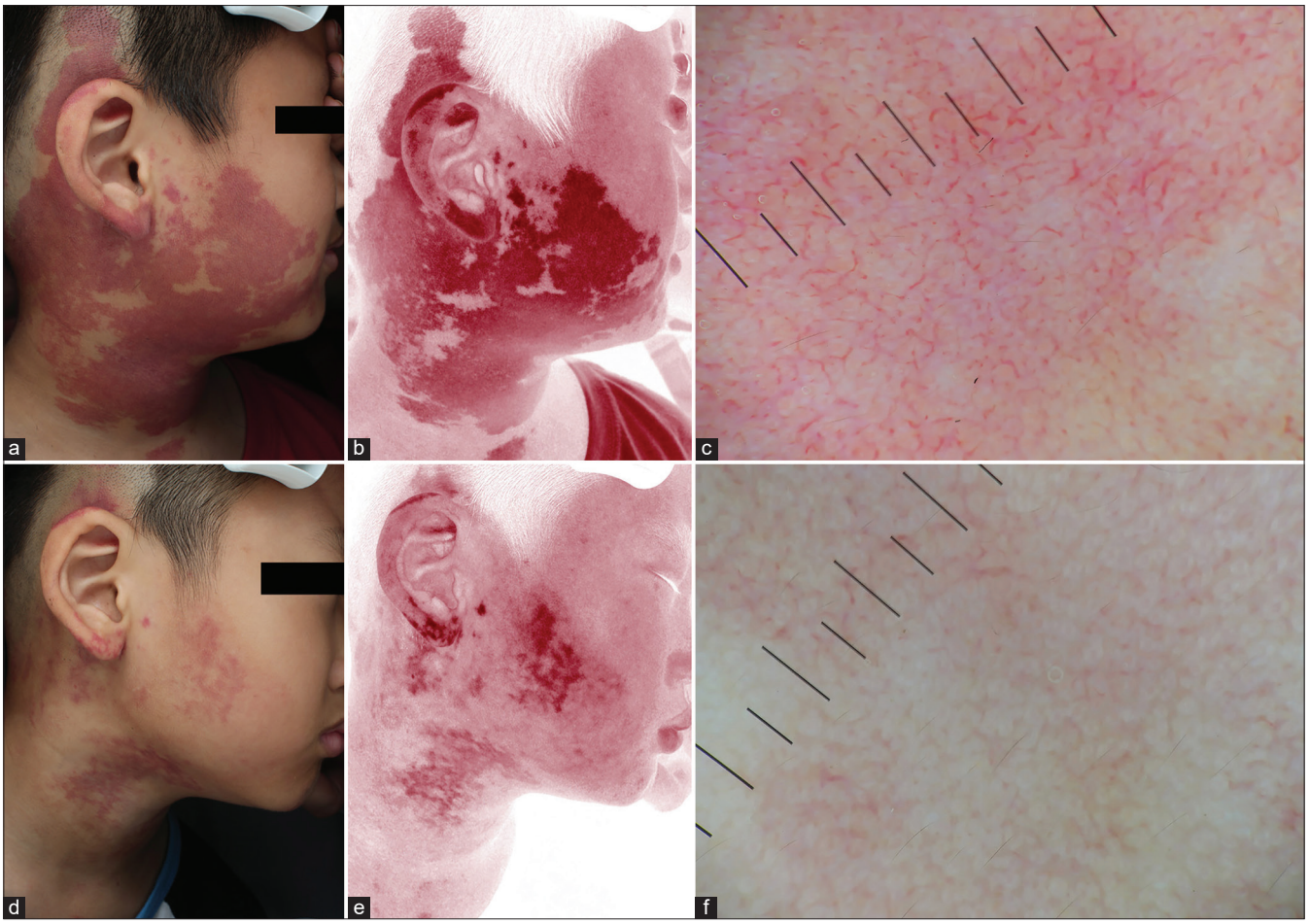

Figure 2: (a) A 8-year-old boy with port wine stains on the right face and neck, (b) a large area of redness in the lesion, (c) many reticular vessels and a few scattered punctate vessels appeared before treatment. (d) the erythema decreased in size and became lighter in color with good improvement after a single treatment, (e) the degree of redness and area size reduced significantly (6500-K standard white light and polarized lights source, VISIA), (f) the density and redness of blood vessels reduced significantly after 8 weeks of a single treatment (DMT-200, polarized, ×20)

alleviated at the eighth week of follow-up and subsided spontaneously within three to six months. A few small blisters appeared in two (1.9%) patients and improved spontaneously within one week. No systemic or allergic adverse reactions were observed. The results of complete blood counts, routine urine test, liver and renal function tests and electrocardiograms were normal in all patients four days and eight weeks after treatment.

Recurrence

All 107 patients were followed up for 14–33 months, and the mean follow-up duration was 21.3 months with no recurrence.

Discussion

The principle of vascular-acting photodynamic therapy is that the photosensitizer forms a peak concentration in the blood immediately after intravenous injection which is quickly absorbed by vascular endothelial cells, and less absorbed by epidermal cells. Then, laser irradiation of a certain wavelength can be selectively absorbed, inducing the generation of singlet oxygen and other reactive oxygen species. This photochemical reaction selectively destroys abnormally expanded capillaries rich in photosensitizers and specifically removes erythema with little damage to the epidermis, thereby producing scar-free results.[8] This is a unique feature of photodynamic therapy that has been confirmed *in vivo* and *in vitro*.[9,10] Qiu *et al.* believed that it could selectively destroy port-wine stains vessels of any size and that all types of port wine stains were sensitive to this therapy, regardless of treatment history.[11] Photodynamic therapy was also effective in pulsed dye laser-resistant port-wine stains, and no recurrence was observed even in a follow-up that was longer than 19 years. The photosensitizer hemoporfin is a new monosomal porphyrin drug with a half-life of about 1.31 h. It is rapidly removed from the body with low toxicity.[12] The light source was a laser with a wavelength of 532 nm and a continuous output mode similar to the absorption peak of 533 nm of hemoporfin which can stimulate the photosensitizer effectively to produce a photosensitive response.

Our study showed that age, anatomical location, type as well as the number of treatment sessions were all closely related

to clinical efficacy. The earlier patients received hemoporfin photodynamic therapy, the better efficacy they achieved. Better efficacy was achieved with in lesions of the lateral part of the face as compared to the central part. The best effect was observed with the pink type, followed by the red type, while the poorest effect was seen with the purple type. The clinical effect of two treatments was significantly better than that of a single treatment.

Early treatment in infants is more effective because of the smaller size of lesions and the thinner skin. The advantages are as follows: (1) less epidermal melanin competing for laser light absorption; (2) less dermal collagen reducing the light backscattered out of the skin and (3) thinner dermis and lower blood volume allowing more light to penetrate.[13] Therefore, we advise early treatment for better efficacy. The efficacy of treatment for the lateral part of the face was better than that for the central part. This was observed even in the same patient. The difference may be related to the thickness and blood flow of the local skin, the diameter and depth of vessels and power density of the laser: (1) the skin in the centrofacial area is thicker than the peripheral area due to abundant sebaceous units;[14] (2) the dilated capillaries of port -wine stains are mainly distributed in the papillary dermis in the lateral part of the face, while in the central part, they are distributed from capillaries to the reticular dermis and even to the subcutaneous tissue; (3) port-wine stains vessels in the lateral area of the face are more superficial and smaller in diameter than those in central areas[15] and (4) the skin of the lateral part of the face is relatively flat and lies in the same plane which makes it easier to ensure the uniformity of laser irradiation. Patients with red type port-wine stains have denser skin tissues and less light transmittance than patients with pink type, while patients with purple type have thicker blood vessel walls, larger vascular diameters and poorer light transmittance. Therefore, the efficacy of treatment in the pink type is better than that in the red and purple types. Although good effect is seen in a single treatment, the overall result is always limited. For severe lesions, multiple treatments are needed to gradually eliminate the pathological vascular network. Qiu *et al.* concluded that repeated treatment is usually necessary for better cosmetic results, especially for purple and proliferative purple lesions.[11]

With little photosensitizer in the epidermal cells, the adverse reactions are mild. Local swelling was a normal treatment response and no special intervention was required. Using cool ice packs in the first 48 h to reduce photothermal damage are very important. The small amount of photosensitizer that remains in the body may cause skin pigmentation. It is advised to avoid strong light and reduce outdoor activities. The doctor should carefully determine the treatment parameters and the proper endpoint of treatment, especially for patients who receive photodynamic therapy for the first time.

Limitations

Our evaluation was limited to the facial port-wine stains in children. No objective measurement data were available.

Conclusion

Hemoporfin photodynamic therapy is safe and effective in children with refractory facial port-wine stains resistant to pulsed dye laser with low incidence of adverse reactions.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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