

Review

Clinical study on hemoporphin PDT for infant facial port-wine stains

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ABSTRACT

Objective: To observe the clinical efficacy and therapeutic response of Hemoporphin photodynamic therapy (PDT) for infant facial port-wine stains (PWS).

Method: Hemoporphin PDT was used to treat 100 cases of infant facial PWS. After receiving Hemoporphin skin test, the cases with a negative skin test result were intravenously injected with Hemiporphin (5 mg/kg) and irradiated under 532 nm LED green light. After treatment, a follow-up visit was paid through WeChat and Dermlink PWS consulting platform, in order to observe the therapeutic response and clinical efficacy.

Result: The follow-up visit showed an effective rate of 98%, including 85 cases of itching (85%), 100 cases of edema (100%), 89 cases of purpura-like change (89%), 33 cases of crust (33%), 2 cases of hyperpigmentation (2%) and 2 cases of scars (2%), with no allergy and other systematic adverse reaction.

Conclusion: Hemoporphin PDT has a high clinical efficacy and response rate in treating infant facial PWS, with slight adverse reactions.

1. Introduction

Port-wine stains (PWS) are a type of congenital capillary malformation at the dermal papillary layer, and often occur on the face, neck and scalp at birth or shortly after birth. In the early age, PWS usually appears as bright red patches. As the age increases, the patches become purplish red. The incidence rate is between 3 and 5‰ [1,2]. According to the color of patch and the skin hyperplasia, PWS can be classified into pink type, purplish red type and nodular thickening type [3,4]. Infant PWS is mostly pink and purplish red. PWS is unlikely to spontaneously fade away. Along with the increase of children's age and cognitive ability, PWS may have an impact on their self-esteem. In fact, PWS shall be treated as early as possible, because the therapeutic efficacy is significant to the physical and mental development of children at the pre-school age. PDT is a diagnostic and therapeutic technique based on the interactions of light, photosensitizer and oxygen. In December 2016, new drug Hemoporphin was launched in China and applied in clinical practice. Our department has applied PDT in treating 100 cases of infant PWS, and reached a satisfactory efficacy. The summary report is as follows:

2. Materials and method

2.1. Clinical data

The 100 cases were outpatients diagnosed as infant PWS at our department from March 2017 to November 2017. They were aged between 1 and 3 years old, with the average age of 1.74 years old, including 60 males and 40 females, 35 cases of pink type PWS and 65 purplish red type PWS, and 24 untreated cases, 60 cases previously treated with pulsed dye laser for 1–18 times, 11 cases previously treated with PDT for 4–6 times and 5 cases previously treated with both laser and PDT.

2.2. Exclusion criteria

Cases with allergic diseases, including those with known to skin photosensitivity, porphyria, known to be allergy to experimental drugs and their chemical structures, scar diathesis, severe hepatic and renal insufficiency, and a history of epilepsy.

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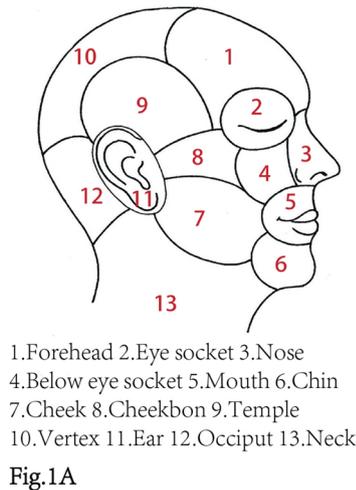
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1.Forehead 2.Eye socket 3.Nose
4.Below eye socket 5.Mouth 6.Chin
7.Cheek 8.Cheekbon 9.Temple
10.Vertex 11.Ear 12.Occiput 13.Neck

Fig.1A



Fig.1B 在企业微信中打开



Fig.1C



Fig.1D

Fig. 1. A Distribution of anatomical locations of facial PWS. Fig. 1B Postoperative follow-up software system on Dermlink PWS consulting platform through WeChat. Fig. 1C System dialogue interface on Dermlink PWS consulting platform through WeChat. Fig. 1D Photos of 1 male patient during follow-up visit on a daily basis.

Table 1
Distribution of 100 cases of infant facial PWS lesions.

No.	Location	Number of cases (n)	Percent (%)
1	Forehead	15	15%
2	Eye socket	43	43%
3	Nose	16	16%
4	Below eye socket	58	58%
5	Mouth	50	50%
6	Chin	18	18%
7	Cheek	73	73%
8	Cheekbone	66	66%
9	Temple	31	31%
10	Vertex	6	6%
11	Ear	4	4%
12	Occiput	10	10%
13	Neck	15	15%

2.3. Equipment

Photosensitizer Hemoporfin was produced by Shanghai Fudan Zhangjiang Bio-Pharmaceutical Co., Ltd. (batch No.20171010); PDT equipment was 532 nm LED green light equipment (LED-3modified machine produced by Wuhan YaGe); digital SLR camera was Canon 70D; photostudio was China-made Chunying CY-200.

Table 2
Therapeutic response of 100 cases of infant facial PWS after HMME-PDT.

	Number of cases (n)	Percent (%)	Number of cases (n)	Percent (%)
Therapeutic response	Yes		No	
Pruritus	85	85.00%	15	15.00%
Edema	100	100.00%	0	0
Visible purpura	89	89.00%	11	11.00%
Crust	33	33.00%	67	67.00%
	Thin crust	27		
	Thick crust	6	18.18%	
Hyperpigmentation	2	2.00%	98	98.00%
Depigmentation	0	0	100	100.00%
Adverse reaction				
Scar	2	2.00%	98	98.00%
Infection	0	0	100	100.00%
Efficacy	98	98.00%	2	2.00%

3. Therapeutic method

The therapeutic regimen of Hemoporfin PDT for infant PWS was approved by the ethics committee of our hospital. The specific operation process is as follows:

3.1. Pre-treatment history-taking

The diagnosed cases were aged between 1 and 3 years old. Their detailed information was registered. Their photos were collected with a fixed digital camera in the studio. On the basis of the distribution of anatomical locations of facial PWS (Fig. 1A), the distribution and color of PWS were recorded, and the body weight of the patients was measured.

3.2. Pre-treatment examination of laboratory indicators

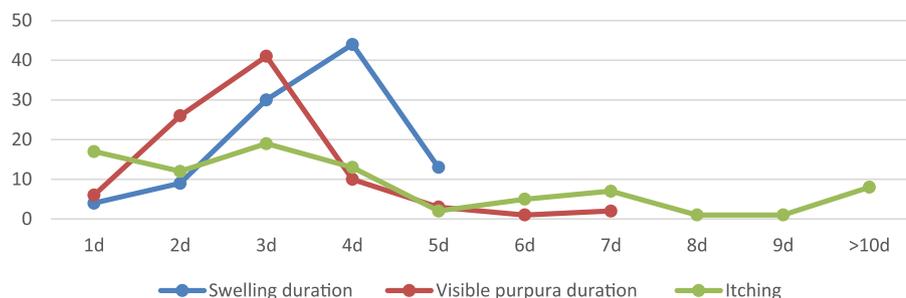
Hepatic function, renal function, blood routine and electrocardiogram; all of the indicators shall be normal before treatment.

3.3. Pre-treatment skin test [4]

Hemoporfin was dissolved with normal saline to the concentration of 125ug/ml. The diluent was intradermally injected into the left or right forearm, and normal saline was used for blank control. Only those with the negative result of skin test could use Hemoporfin.

Table 3
Therapeutic response of 100 cases of infant facial PWS after HMME-PDT.

	Swelling duration	Visible purpura duration	Itching
1d	4	6	17
2d	9	26	12
3d	30	41	19
4d	44	10	13
5d	13	3	2
6d		1	5
7d		2	7
8d			1
9d			1
> 10d			8



3.4. Hemoporfin PDT

Before treatment, adhesive tape was pasted along the edge of the treatment area, and normal skin outside of the treatment area was covered with double layers of black fabrics. The treatment area was fully exposed in the same horizontal plane. The equipment was thoroughly debugged and maintained in a normal status. The irradiating light was vertical with the treatment area. The general dosage of photosensitizer was 5 mg/kg; the dosage of each case was calculated based on the weight. The photosensitizer was slowly injected. The irradiation dosage was generally 75–95 MW/cm². The irradiation time was set in advance. The irradiation dosage and the irradiation time were selected based on such factors as the skin and age of each case.

3.5. Post-treatment follow-up visit

After treatment, we asked the patients’ parents to regularly send the patients’ photos through WeChat and Dermlink PWS consulting platform, in order to give them postoperative nursing guidance, record the

patients’ therapeutic response, and make the meta-analysis.

3.6. Clinical efficacy evaluation [4]

The efficacy was observed 2 months later after treatment. The cases were photographed under a fixed light source, and their photos before and after treatment were compared to evaluate the efficacy. Effective: Partial depigmentation in the treatment area (degree of improvement ≥20%); Ineffective: color unchanged or mostly unchanged in the treatment area (degree of improvement < 20%). Post-treatment crust thickness: thin crust: thickness < 0.5 mm, thick crust: thickness ≥ 0.5 mm.

3.7. Statistical method

SPSS 22.0 statistical software was used for data analysis.



Fig. 2. Clinical efficacy after PDT treatment. Fig. 2 A 2B 1 case of purplish red type PWS at the right face before and after 1 PDT treatment (female). Fig. 2 C 2D 1 case of infant purplish red type PWS at the left face before and after one PDT treatment (male).



Fig. 3. A 1 case of pink type PWS at the left face before PDT treatment (female, 1 year old). **Fig. 3 B** Obvious edema 1 day later after PDT treatment. **Fig. 3 C** Obvious purple spots and purpura-like change at the face 5 days later after PDT treatment. **Fig. 3 D** Thin crust in treatment area 2 weeks later after PDT treatment. **Fig. 3 E** Reduction of PWS area by above 90% 2 months later after PDT treatment. **Fig. 3 F** Postoperative follow-up visit through WeChat and Dermlink PWS consulting platform.

4. Result

According to the statistical analysis based on the distribution of anatomical locations of the 100 cases of infant PWS (Fig. 1A), 73% were distributed at the cheeks, 66% were distributed at the cheekbones, and 58% were distributed below the eye sockets; these three locations were the most commonly seen in facial PWS. The distribution of locations is shown in See Table 1. We paid follow-up visits to all of the cases through WeChat and Dermlink PWS consulting platform (Fig. 1B, C, D), in a bid to observe and record the therapeutic response after treatment. Specifically, 85% of the cases suffered from itching; all of the cases suffered from varying degrees of edema, which generally lasted for 1 to 5 days; 89% had purpura-like change, which lasted for 1 to 7 days. After treatment, 33 cases had crusts, including 25 cases of thin crusts and 8 cases of thick crusts, which lasted for 2 to 3 weeks in general; 2 cases had hyperpigmentation; and 2 cases had scars, accounting for 2%. Two

months later after treatment, the efficacy evaluation showed an effective rate of 98% (Tables 2 and 3, Fig. 2A, B, C, D). No other systemic adverse reaction was observed in all of the cases after PDT treatment.

5. Discussion

Infant PWS is a type of congenital vascular malformation at the dermal layer at birth, and would not be spontaneously regressed. It often occurs on the face or neck, where affect patients' appearance and thus bring huge psychological trauma to the children and their parents. In the cases of infant PWS, dermal capillaries and venules are gradually expanded and darkened with age, and the lesions become thickened and even verrucous hyperplasia after the middle age [5,6]. Therefore, it is suggested to treat PWS at the early age. After new drug Hemoporfin was launched in China, our team has summarized some operational experiences in clinical practice [4], and reported 3 cases of PWS treated

with PDT that achieved a good efficacy [7]. Between September and November 2017, we treated 100 cases of infant PWS using PDT, then paid follow-up visits to them, analyzed the common responses, and summarized the clinical efficacy, in order to provide the basis for better treatment of infant PWS with PDT in the future.

The principal theory of Hemoporphin photodynamic therapy (HMME-PDT) for PWS is that PDT has a targeted destructive effect on focal vascular walls. After intravenous injection, Hemoporphin immediately reaches the concentration peaks in the blood, and is absorbed rapidly by vascular endothelial cells but less by epidermal cells. At that moment, 532 nm green light irradiation is provided to excite the photosensitizer to generate the photochemical reaction and produce singlet oxygen and other light toxic substances, which can cause swelling, degeneration and necrosis of vascular endothelial cells, and achieve the therapeutic effect [8,9]. At the same time, laser is hard to penetrate and damage deep dermal tissues. Among the 100 infant PWS cases aged between 1 and 3 year old in this study, the effective rate attained 98% after 1 PDT treatment. After treatment, itching and edema were common responses, and 85% of cases suffered from itching and scratched the treatment area. Therefore, it was necessary to carefully look after the children for fear of any skin damage or infection caused by scratching. Itching usually occurred within 2 weeks. After treatment, all of the patients suffered from edema, and 75% of them had edema on the day of treatment. The degree of edema varied from case to case. Specifically, edema was generally mild at the nose and cheekbone, where skin soft tissues are relatively thin; whereas edema was generally severe at the cheek and other locations with thick skin soft tissues (Fig. 3A, B). In general, edema does not need to be specially treated, and can spontaneously regress 3 to 5 days later (Table 3). During the study, we also found that some cases also had edema at the opposite face that was untreated. And 89% of cases had purpura-like change after treatment, and visible purpura 3 days later (Fig. 3C), which lasted for about a week. After treatment, some cases had crusts. Among them, 8 cases had thick crusts, in which 2 cases exposed the treatment area to water, and 3 cases suffered from eczema before treatment and were not infected after daily application with iodophor; and 25 patients had thin crusts, which did not need any special treatment and would spontaneously fall off (Fig. 3D). After treatment, we observed the cases' photos through WeChat and Dermlink PWS consulting platform every day, monitored their nursing status, and provided better guidance for the postoperative treatment (Fig. 3E, F). During the recovery after treatment, 2 cases had scars, which were caused by scratching at crusts.

Operation is very important in PDT for infant PWS. PDT's efficacy is closely correlated with many factors, and its therapeutic mechanism involves interactions of light, photosensitizer, oxygen and lesion tissue under irradiation [10,11]. In addition to the dosages of photosensitizer and light, PDT's efficacy is also closely associated with the type of tissue at the treatment location, age and past treatment history. As for the treatment for infant PWS, the dosages of photosensitizer and light shall be determined based on many factors. The first treatment shall begin with a low dosage for fear of any skin damage and scar caused by high dosage. Particularly for facial PWS cases of scar diathesis, scars caused by malpractice have a serious impact on their appearance. In addition, the skin sensitivity to PDT greatly varies from case to case. As for the cases that receive PDT for the first time, doctors shall determine the treatment dosage prudentially. During treatment of infant PWS with PDT, close attention shall be paid to the response in the treatment area. When depigmentation or dark purple spots quickly occur in the treatment area, the irradiation time could be properly shortened; otherwise, the irradiation time shall be prolonged, in order to prevent the inefficiency due to insufficient light dosage. During the whole process of treatment, the treatment operation specifications shall be strictly observed, so as to ensure a better clinical efficacy.

The dynamic follow-up visit is important after treatment of infant PWS with PDT. Along with the rapid development of Internet + healthcare in China, after treatment, doctors could pay the follow-up visit to patients through WeChat and Dermlink PWS consulting platform; and the patients' parents could consult doctors about postoperative problems through WeChat platform. In case of any response that the parents are unable to handle, they could send the patients' photos to doctors and seek help from doctors at any time; in turn, doctor could give correct nursing guidance to the patients through WeChat, so as to reduce the occurrence of adverse reactions and better guarantee the therapeutic efficacy. In the meantime, doctors could also make summarization and analysis of the photos sent by patients, in order to provide parameter basis for the next treatment.

Hemoporphin PDT is one of the world's most promising therapies for infant facial PWS. PDT has complicated operation specifications and involves multiple impacting factors. To guarantee a better therapeutic efficacy and safety, and avoid the occurrence of adverse reactions, doctors shall formulate individualized treatment parameters for each patient, and strictly follow the treatment operation specifications.

6. Conclusion

According to our findings, HMME-PDT could effectively treat infant facial PWS. To achieve a satisfactory clinical efficacy, efforts shall be made to formulate individualized treatment parameters before treatment, strictly observe the treatment operation specifications during treatment, and provide follow-up visits and careful nursing after treatment.

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