Journal of Biomedical Optics

SPIEDigitalLibrary.org/jbo

New optional photodynamic therapy laser wavelength for infantile port wine stains: 457 nm

Ying Wang
Zhaohui Zuo
Ying Gu
Naiyan Huang
Rong Chen
Buhong Li
Haixia Qiu
Jing Zeng
Jianguo Zhu
Jie Liang

SPIE

New optional photodynamic therapy laser wavelength for infantile port wine stains: 457 nm

Ying Wang,[a] Zhaohui Zuo,[b] Ying Gu,[a] Naiyan Huang,[a] Rong Chen,[c] Buhong Li,[c] Haixia Qiu,[a] Jing Zeng,[a] Jianguo Zhu,[a] and Jie Liang[a]
[a]Chinese People's Liberation Army General Hospital, Department of Laser Medicine, Beijing 100853, China
[b]Beijing Shuguang Aerospace Electrical Co. Ltd., No. J.5 Jingshun Road, Chaoyang District, Beijing 100028, China
[c]Fujian Normal University, Institute of Laser, Key Laboratory of Photonic Technology of Fujian Province, No. 8 Shangshan Road, Cangshan District, Fujzhou 350007, China

Abstract. To expand the optional laser wavelengths of photodynamic therapy (PDT) for port wine stain (PWS), the feasibility of applying a 457 nm laser to the PDT for infantile PWS was analyzed by mathematical simulation and was validated by clinical experiment. Singlet oxygen yield of 457 nm PDT or 532 nm PDT in an infantile PWS model and an adult PWS model was theoretically simulated. Fifteen PWS patients (14 infants and 1 adult) with 40 spots were treated with 457 nm (20 spots) and 532 nm (20 spots), respectively, in two PDT courses. Simulation results showed that under the same power density and irradiation time, singlet oxygen yield of 457 nm PDT and 532 nm PDT are similar in infantile PWS vessels. Yet, in adult PWS vessels, singlet oxygen yield of 457 nm PDT is lower than 532 nm PDT. Clinical outcomes showed that no statistic difference existed between 457 nm PDT and 532 nm PDT for infantile PWS. The result of this study suggested that 457 nm wavelength laser has the potential to be applied in PDT for infantile PWS. [DOI: 10.1117/1.JBO.17.6.068003]

Keywords: photodynamic therapy; mathematical simulation; port wine stain.

Paper 12081 received Feb. 6, 2012; revised manuscript received Apr. 19, 2012; accepted for publication Apr. 27, 2012; published online Jun. 6, 2012.

1 Introduction

Port wine stain (PWS) is a congenital vascular malformation histologically characterized by ectatic capillaries in papillary layer of the dermis. It usually appears at birth and scarcely disappears spontaneously. PWS is usually classified as pink, red, or purple according to the color, as the classification of PWS has still not been unified. In most cases, PWS is pink or red at birth. As the age increases, the PWS color tends to become darker, and the involved skin may become thicker, even nodular changes. Histologically, the mean vessel area (dermal area composed of vessels) increased with age, as well as vessel number, mean wall thickness, and mean vessel depth also minimally increased.[1]

Photodynamic therapy (PDT) with the advantage of dual selectivity has been applied in the treatment of PWS for 20 years.[2] Our clinical experiences showed that it is effective for all types of PWS. Photocarcinorin (PSD-007) combining 532 nm wavelength laser is the most commonly used strategy in China.[2–4] With the deep insight of PDT dose-response relationship, people recognized that it is very much worth making individual PDT scheme to meet needs of diversity of PWS histological structure. For example, laser wavelength 510 nm which has a lower absorption for hemoglobin and higher molar extinction coefficient for PSD-007 than 532 nm can be applied to the treatment of PWS with deeply located ecstatic vessels.[5]

As is known, PSD-007 has a higher molar extinction coefficient around 400 nm than at 532 nm. However, melanin and hemoglobin also has higher absorption around these wavelengths, and scatter coefficient around these wavelengths is higher than that at 532 nm. It suggested that these wavelengths may penetrate more superficially in skin than 532 nm, and the number of photon deposited in target vessels may be lower. Whether these wavelengths are suitable for PWS PDT or only suitable for certain types of PWS attracts wide notice, and needs further research.

Previous research has indicated that mathematical simulation can facilitate the comprehension of complicated interrelationship between laser, photosensitizer, and oxygen in PDT reaction.[6–9] In the present study, we choose 457 nm at which the excited efficiency of photosensitizer (PSD-007) is similar to 532 nm (Fig. 1). Firstly, the light distribution of 457 and 532 nm in infantile or adult PWS skin model was simulated, then singlet oxygen yield of 457 or 532 nm mediated PDT at the same photosensitizer dosage was compared. Finally, clinical experiment was done to compare the efficiency of 457 and 532 nm PDT.

2 Materials and Methods

2.1 *Mathematical Simulation*

2.1.1 *Port wine stains skin geometry*

The PWS skin geometry used in the present modeling was previously described.[5] It consists of stratum corneum, epidermis above the basal melanin layer, basal melanin layer, and dermis embedded with ectatic vessels (Fig. 2). The total thickness of PWS skin model is 1300 μm, not including subcutaneous tissue below dermis. Vessels are parallel to Y axis. Laser beam diameter is 1 mm at x, $y = 0$ μm.

Address all correspondence to: Y. Gu, Chinese People's Liberation Army General Hospital, Department of Laser Medicine, No. 28 Fuxing Road, Haidian District, Beijing 100853, China. Tel: 008610 66939394; Fax: 008610 68222584; E-mail: guyinglaser@sina.com

0091-3286/2012/$25.00 © 2012 SPIE

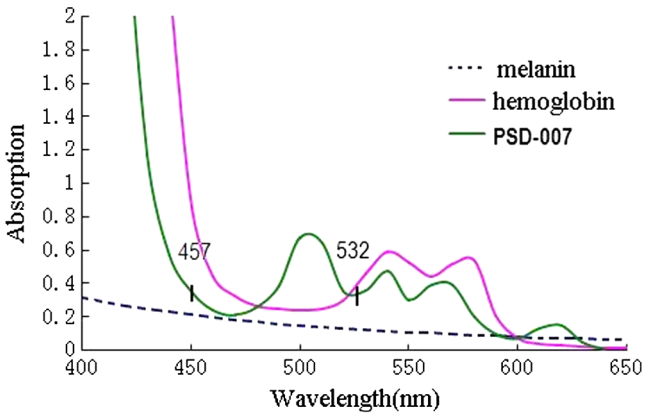

Fig. 1 Schematic diagram of the absorption spectra of PSD-007, hemoglobin, and melanin in water. The molar extinction coefficient of PSD-007 at 457 nm is similar to that at 532 nm. The molar extinction coefficient of hemoglobin at 457 nm is slightly higher than that at 532 nm. The molar extinction coefficient of melanin at 457 nm is higher than that at 532 nm.

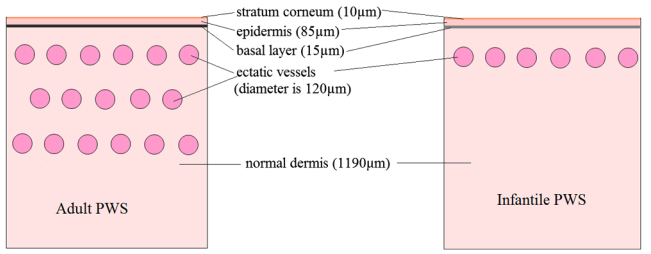

Fig. 2 Geometry model of PWS skin. It consisted of stratum corneum, epidermis above the basal melanin layer (with less melanin, $m\% = 0.1\%$), basal melanin layer (containing lots of melanin) and dermis embedded with ectatic vessels. Infantile PWS model contains one layer vessels, and adult PWS contains three layer vessels. The separation between epidermal-dermal junction and the up wall of the first layer capillary was set at 100 μm. The vertical separation between two vessel layers is 100 μm, and the lateral separation between two capillaries were 60 μm. The total thickness of skin is 13000 μm, not including the subcutaneous tissue below the dermis.

As Ref. 10 reported, the thickness of stratum corneum and epiderm in infantile skin is similar to adult skin. The main difference is that the size and volume of stratum corneum cells in infantile skin is more uniform, and the number of melanosome in basal layer of epidermis is less. It can be supposed that the scatter of stratum corneum and the melanin content in epidermis is lower in infantile skin. The total epidermis melanin content ($m\%$ was set at 2% for adult PWS and 0.5% for infantile PWS.

2.1.2 *Skin optical properties*

Skin optical properties of PWS skin were calculated according to Refs. 11–13 and were listed in Table 1.

2.1.3 *Simulation of PDT singlet oxygen yield*

The mechanism of PDT mediated vascular effect is based on the dual selectivity distribution of photosensitizer and laser in target vessels. At a short drug-light interval, photosensitizer accumulated predominantly in vascular. Highly reactive oxygen species (such as singlet oxygen) generated through the reaction between light and photosensitizer oxidize the membrane of vascular endothelial cell, leading to vascular stasis, thrombus formation or permanent vessel occlusion. The simulation model of singlet oxygen yield in PWS tissue and simulation method based on photochemical reaction of PDT was previously published.[5] In the present study, the singlet oxygen yield in infantile PWS skin and adult PWS skin was simulated respectively.

2.2 *Clinical Experiment*

2.2.1 *Patients*

Fifteen patients with congenital PWS were recruited for this study. All of them were undergoing PDT treatment at the Department of Laser Medicine of Chinese PLA General Hospital. Informed consent was obtained from each patient or their guardian. The demographic data of PWS patients was listed in Table 2.

2.2.2 *PDT procedure*

Each patient received twice PDT treatments (one is 457 nm and the other is 532 nm) at an interval of at least eight weeks. 457 nm PDT was applied in the first course, 532 nm PDT was applied in the second course. Or two PDT courses were performed in an opposite sequence. The number of spots that first time treated by 457 nm is 11, while the number of spots that first time treated by 532 nm is 9. The laser dosage and photosensitizer dosage is similar in the two PDT courses. The therapeutic outcomes of two PDT courses in the same person were compared.

2.2.3 *PDT treatment*

Domestic photosensitizer PSD-007 (Photocarcinorin) and 532 nm/457 nm solid state laser (Beijing Newraysing Laser Technology Co., Ltd.) was applied in PDT treatment. PSD-007 was administered by intravenous injection at a dose of 4–5 mg/kg body weight. Laser irradiation (100 mW/cm^2, $20 \sim 40$ min) started immediately after PSD-007 injection.

2.2.4 *Clinical evaluation of PDT efficacy*

There are no international standard evaluation criteria available to assess the effectiveness of PDT for PWS. In this study, we used the criteria suggested by Gilchrest for the assessment of clinical outcomes of laser therapy.[14] Similar criteria were often used by other physicians in China.[15,16] Treatment outcomes were evaluated $8-12$ weeks after PDT. Lesion sites were examined visually and photographs were taken before and after treatment. Clinical outcomes were graded as Table 3.

2.2.5 *Statistical analysis*

Statistical analysis was performed using Stata 7.0 software. The treatment outcomes of 457 nm PDT and 532 nm PDT was compared using Spearman's rank correlation analysis. A difference was considered to be statistically significant with P values < 0.05.

Table 1 PWS skin optical properties used in the present study.

Wavelength (nm)	Optical properties	Sc	Epidermis	Basal layer	Dermis	Blood
457	μ_a (cm^{-1})	202	1.98	50 ($m\% = 2\%$) △ 10 ($m\% = 0.5\%$)	3.1	200
	μ_s (cm^{-1})	2200 △ 1000	263	263	263	500
	g	0.95	0.75	0.75	0.75	0.98
	n	1.45	1.4	1.4	1.4	1.33
532	μ_a (cm^{-1})	181	1.1	34 ($m\% = 2\%$) △ 8 ($m\% = 0.5\%$)	2.6	206
	μ_s (cm^{-1})	2200 △ 1000	184.4	184.4	184.4	500
	g	0.93	0.774	0.774	0.774	0.98
	n	1.45	1.4	1.4	1.4	1.33

stratum corneum, the unit of μa and μs is cm^{-1}, m%: percentage content of melanin in the whole epidermis. △ is the optical properties of infant which is different from adult, the other is similar to adult.

Table 2 Demographic data.

		Number of spots		
Age (y)	Cases	457 nm	532 nm	Total
1 to 6	9	12	12	24
7 to 17	5	7	7	14
18 to 30	1	1	1	2
Total	15	20	20	40

Table 3 Criteria of treatment outcome.

Grade	Clinical description
Excellent	Become normal skin
Good	Slight residual color
Fair	Obvious lightening
Poor	Minimal lightening

3 Results

3.1 *Light Distribution and Singlet Oxygen Yield of 457 nm PDT and 532 nm PDT in Infantile PWS Tissue*

Light fluence rate of 457 nm laser at epidermis of infantile PWS was higher than that of 532 nm laser. As the 457 nm laser has larger melanin absorption and back scatter, more 457 nm light was back scattered to the superficial layer of skin. Light fluence rate of 457 nm laser at the top side of the blood vessels close to skin surface was slightly higher than 532 nm, and slightly lower than 532 nm at the inferior wall of vessels [Fig. 3(a) and 3(b)]. Light fluence rate of two wavelength laser was similar in the center part of vessels. In deep dermis, light fluence rate of 457 nm laser is lower than 532 nm. This result showed the penetration depth of 457 nm laser in infantile PWS is slightly shallower than 532 nm laser, more 457 nm laser was deposited in superficial layer of PWS skin.

The feature of singlet oxygen yield in PWS vessels under 457 nm PDT and 532 nm PDT is similar. Singlet oxygen is mainly generated in PWS vessels. With the same light dose (100 mW/cm^2, 40 min), 457 nm PDT generate a slightly lower singlet oxygen yield in PWS vessels than 532 nm PDT [Fig. 4(a) and 4(b)].

In addition, the singlet oxygen yield of 457 nm PDT in PWS with deeply located vessels (500 μm below the epidermal-dermal junction) was simulated. The result showed that singlet oxygen yield of 457 nm PDT in PWS vessels is much lower than 532 nm PDT. This suggested that 457 nm PDT is not suitable for PWS with deeply located vessels (Fig. 5).

3.2 *Light Distribution and Singlet Oxygen Yield of 457 nm PDT and 532 nm PDT in Adult PWS Tissue*

As there were more vessels in adult PWS, more light (both 457 and 532 nm) was deposited in three layer vessels than in infantile skin, and less light was deposited in stratum corneum and epidermis than in infantile skin. The result showed that light fluence rate of 457 nm laser at epidermis is similar to 532 nm laser in adult PWS. Though the absorption of melanin is higher at 457 nm, the effect of melanin absorption on light fluence rate in epidermis is overwhelmed by the bigger hemoglobin absorption in vessels. Light fluence rate of 457 nm laser at vessels is lower than 532 nm in adult PWS, especially at the second and third layer vessels [Fig. 3(c) and 3(d)]. In deep dermis, light fluence rate of 457 nm laser is lower than 532 nm. This result

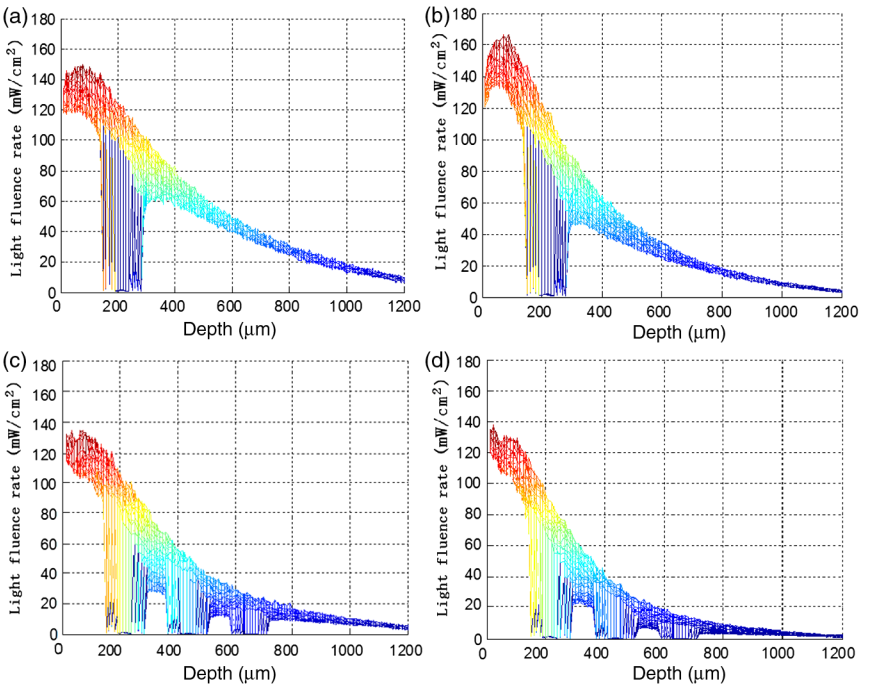

Fig. 3 Spatial profiles of light distribution in PWS skin model. (a) 532 nm PDT for infantile PWS. (b) 457 nm PDT for infantile PWS. Light fluence rate of 457 nm laser at epidermis is higher than 532 nm. Light fluence rate of 457 nm laser at vessels is slightly lower than 532 nm, especially at the inferior wall of vessels. (c) 532 nm PDT for adult PWS. (d) 457 nm PDT for adult PWS. Light fluence rate of 457 nm laser at epidermis is similar to 532 nm. Light fluence rate of 457 nm laser at vessels is lower than 532 nm. Light fluence rate of 457 nm laser at vessels is lower than 532 nm, especially at the second and third layer vessels.

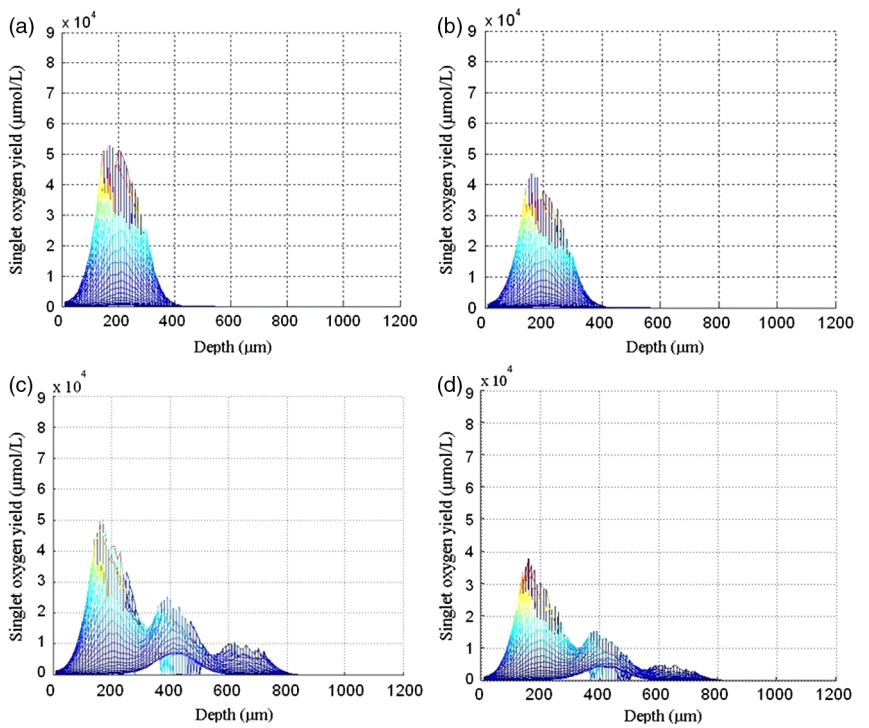

Fig. 4 Spatial profiles of singlet oxygen yield in PWS skin model. (a) 532 nm PDT for infantile PWS. The singlet oxygen yield in the superior wall and the inferior wall of PWS vessels were 5×10^4 μmol/L and 2.6×10^4 μmol/L, respectively. (b) 457 nm PDT for infantile PWS. The singlet oxygen yield in the superior wall and the inferior wall of PWS vessels were 4.2×10^4 μmol/L and 2×10^4 μmol/L, respectively. (c) 532 nm PDT for adult PWS. The singlet oxygen yield in the superior wall and the inferior wall of the first layer PWS vessels were 5×10^4 μmol/L and 2×10^4 μmol/L, respectively. (d) 457 nm PDT for adult PWS. The singlet oxygen yield in the superior wall and the inferior wall of the first layer PWS vessels were 3.8×10^4 μmol/L and 1.8×10^4 μmol/L, respectively.

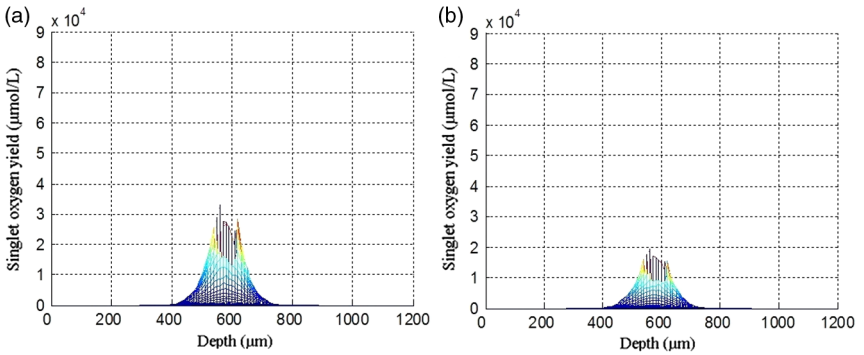

Fig. 5 Spatial profiles of singlet oxygen yield in infantile PWS skin model with deeply located vessels. (A) 532 nm PDT. (B) 457 nm PDT. Vessels were located in 500 μm below the epidermal-dermal junction. Singlet oxygen yield of 457 nm PDT in vessels is significantly lower than 532 nm PDT.

also showed the penetration depth of 457 nm laser in adult PWS is shallower than 532 nm laser.

Singlet oxygen yield of 457 nm PDT in the superior wall and the inferior wall of the first layer PWS vessels is lower than 532 nm PDT. Moreover, the downtrend of singlet oxygen yield in the second and third vessel layer of 457 nm PDT is more distinct than 532 nm PDT [Fig. 4(c) and 4(d)].

3.3 *Clinical Outcomes*

3.3.1 *Treatment outcome*

Clinical outcomes of 40 spots were listed in Table 4. In 457 nm group, 10% of the spots showed a good response, 25% showed a fair response, and 65% showed a poor response. In 532 nm group, 15% of the spots showed a good response, 45% showed a fair response and 40% showed a poor response. It seems that the outcome of 457 nm PDT was slightly poorer than 532 nm PDT, but such difference was not statistically significant ($P > 0.05$).

3.3.2 *Scab after PDT*

The scab rate after PDT was listed in Table 5. Only thin scurf presented in 3 (15%) of the spots in 457 nm group. While thin scurf and thin scab occurred in 9 (45%) and 4 (20%) of the spots, respectively, in 532 nm PDT group. This difference is statistically significant ($P < 0.01$).

Table 4 The treatment outcome of 457 nm PDT and 532 nm PDT.

	Treatment outcome				
	Poor	Fair	Good	Excellent	Total
457 nm	13	5	2	0	20
532 nm	8	9	3	0	20

Table 5 Scab after 457 nm PDT and 532 nm PDT.

	Grade of scab			
	No scab	Thin scurf	Thin scab	Thick scab
457 nm	17	3	0	0
532 nm	7	9	4	0

3.3.3 *Side effects*

Patients were told to took precaution and avoid sunlight exposure for one month. No photosensitivity reaction and no hyperpigmentation occurred in the two groups. No scar occurred in 457 nm group. Tiny scar dot appeared in four patients as a result of careless tearing off the scab.

4 Discussion

Individuation of PDT dosimetry is a developing trend for PDT clinical application.[17] According to the diversity of PWS histological structure (with different vascular depth or vascular area), more alternative laser wavelengths should be available. Infantile skin had less melanin and better translucency, lower light dose is needed, as there are only 532, 578, and 510 nm laser wavelengths available in clinical for PDT of PWS. Light dose for infantile PWS was adjusted by changing laser power density from the adult used 100 mW/cm^2 to 80 mW/cm^2 (Ref. 4) or shortening irradiation time. Moreover, infantile PWS has shallower located vessels and less vascular area. Shorter laser wavelength may have the potential to be used in infantile PWS.

In this study, the main difference between infantile PWS and adult PWS was taken into consideration, such as melanin content in epidermis, vascular area, and vascular depth in dermis. The simulation results and clinical outcome of this study demonstrated the feasibility of applying 457 nm to the PDT of infantile PWS. Theoretically, melanin absorption at 457 nm is higher than at 532 nm, nevertheless, there is less melanin in infantile epidermis, the effect of melanin absorption on the difference of 457 nm and 532 nm laser distribution in infantile epidermis might be ignored. The treatment outcome of 39 spots in infantile PWS patients indicated that there is no significant difference between 457 nm PDT and 532 nm PDT. 457 nm PDT with a lower occurrence of scab may reduce the risk of tiny scar left by careless tearing of the scab, and simplify the postoperative care.

As adult skin has a more rough stratum corneum and more melanin in epidermis, the transparency of adult skin is not as good as infant's. Notwithstanding, the photosensitizer excited efficiency at 457 nm is similar to 532 nm, less light is deposited in PWS vessels at 457 nm. Singlet oxygen yield of 457 nm PDT in adult PWS is lower than 532 nm PDT. In the initial stage

of this study, four adult PWS patients received 457 nm PDT (data was not displayed here). For three adult PWS patients, no significant color blanching was obtained. Nevertheless, a 50% ∼ 75% clear of PWS color was obtained in one fair-skined adult female patient (18-years-old) with PWS pink color, when she was treated for the first time. In the following treatment, 532 nm PDT was used, and good treatment outcome was also obtained. It suggested that 457 nm PDT might also be effective for mild type PWS in fair-skinned adult in the initial PDT courses. There is also severe type PWS in infancy (extensive macula in dark purple color or macula with increased thickness). For such patients, neither PDT nor pulsed laser treatment can gain complete response. Such PWS was not taken into consideration in the present study. As only a few adult patients were recruited in this study, a bigger sample size of adult PWS may prove the above hypothesis. In view of the poor therapeutic outcome predicted for adult, infantile patients were mainly recruited in the present study.

Previous animal experiment and clinical experience have shown that laser wavelength at green and yellow bands are suitable for porphyrin-based photosensitizer mediated PDT of PWS. However, laser wavelength at red band is not suitable.[7,18] Currently, laser wavelengths 532, 510, and 578 nm are usually used as light source for PDT of PWS. Blue light is seldom used. This study give us a hint that red-shifting of the max absorption peak from 400 nm to 500 nm or enhancing the absorption around 500 nm by modifying the chemical structure of porphyrin-based photosensitizer has the possibility of increasing PDT efficiency for PWS, especially for PWS with superficially located vessels.

5 Conclusion

457 nm PDT is as effective as 532 nm PDT for pink or red flat PWS in infant. 457 nm wavelength laser has the potential to be applied in PDT for infantile PWS and pink PWS in fair-skinned adult. Since the small sample size in the present study, a further large-scale study is required to confirm the efficiency of 457 nm PDT for PWS and its indications.

Acknowledgments

This project was supported by the National Natural Science Foundation of China (Nos. 60878055, 61108078, and 61036014).

References

1. S. H. Barsky et al., "The nature and evolution of port wine stains: a computer-assisted study," *J. Invest. Dermatol.* **74**(3), 154–157 (1980).
2. K. H. Yuan et al., "Photodynamic therapy in treatment of port wine stain birthmarks—recent progress," *Photodiagnosis Photodyn. Ther.* **6**(3–4), 189–194 (2009).
3. Z. Huang, "Photodynamic therapy in China: over 25 years of unique clinical experience," *Photodiagnosis Photodyn. Ther.* **3**(2), 71–84 (2006).
4. H. X. Qiu et al., "Twenty years of clinical experience with a new modality of vascular-targeted photodynamic therapy for port wine stains," *Dermatol. Surg.* **37**(11), 1603–1610 (2011).
5. Y. Wang et al., "Choosing optimal wavelength for photodynamic therapy of port wine stains by mathematic simulation," *J. Biomed. Opt.* **16**(9), 098001 (2011).
6. N. Y. Huang et al., "Influence of drug-light-interval on photodynamic therapy of port wine stains—simulation and validation of mathematic models," *Photodiagnosis Photodyn. Ther.* **5**(2), 120–126 (2008).
7. N. Y. Huang et al., "Influence of laser wavelength on the damage of comb's vasculature by photodynamic therapy—simulation and validation of mathematical models," *Lasers. Med. Sci.* **26**(5), 665–672 (2011).
8. L. R. Jones et al., "Monte carlo model of stricture formation in photodynamic therapy of normal pig esophagus," *Photochem. Photobiol.* **85**(1), 341–346 (2009).
9. B. Liu, T. J. Farrell, and M. S. Patterson, "A dynamic model for ALA-PDT of skin: simulation of temporal and spatial distributions of ground-state oxygen, photosensitizer and singlet oxygen," *Phys. Med. Biol.* **55**(19), 5913–5932 (2010).
10. C. H. Liu, "Structure and function of infantile skin," *J. Clin. Dermatol.* **32**(3), 172–173 (2003).
11. T. Dai et al., "Comparison of human skin opto-thermal response to near-infrared and visible laser irradiations: a theoretical investigation," *Phys. Med. Biol.* **49**(21), 4861–4877 (2004).
12. S. L. Jacques, *Skin Optics*, Oregon Medical Laser Center News, Jan 1998, http://omlc.ogi.edu/news/jan98/skinoptics.html.
13. M. J. van Gemert et al., "Skin optics," *IEEE. Trans. Biomed. Eng.* **36**(12), 1146–1154 (1989).
14. B. A. Gilchrest, S. Rosen, and J. M. Noe, "Chilling port wine stains improves the response to argon laser therapy," *Plast. Reconstr. Surg.* **69**(2), 278–283 (1982).
15. Y. Wang et al., "Fluorescence monitoring of a photosensitizer and prediction of the therapeutic effect of photodynamic therapy for port wine stains," *Exp. Biol. Med.* **235**(2), 175–180 (2010).
16. Y. Gu et al., "A clinic analysis of 1216 cases of port wine stain treated by photodynamic therapy," *Chin. J. Laser Med. Surg.* **10**(2), 86–89 (2001).
17. T. C. Zhu and J. C. Finlay, "The role of photodynamic therapy (PDT) physics," *Med. Phys.* **35**(7), 3127–36 (2008).
18. J. S. Nelson et al., "Photodynamic therapy of hypervascular cutaneous tissues in animal models using porphyrin or phthalocyanine activated by red light," *Proc. SPIE* **1200**, 154–163 (1990).