Treatment of pulsed dye laser–resistant port wine stain birthmarks

Zaid F. Jasim, MRCP,[a] and Julian M. Handley, MD, FRCP[b]
Belfast, United Kingdom

The concept of selective photothermolysis with the 577-/585-nm pulsed dye laser (PDL) revolutionized treatment of relatively common port wine stain (PWS) birthmarks. The majority of PWS can be significantly lightened with the PDL. However, few PWS are lightened completely with PDL and up to 20% hardly lighten at all. PDL-resistant PWS exist in any large cutaneous laser practice and constitute a difficult management problem. This article discusses the proposed cause, and currently available and emerging options for PDL-resistant PWS. These include higher power, longer wavelength, variable pulse width lasers with selective epidermal cooling such as 595-nm PDL, 755-nm alexandrite, 810-nm diode, 1064-nm neodymium:yttrium-aluminum-garnet, and intense pulse light systems. Other promising modalities include topical and systemic photodynamic therapy, electrical optical synergy technology, pulse stacking of similar or differing wavelengths, use of optical clearing agents in conjunction with laser, and erbium laser epidermal stripping before laser treatment. (J Am Acad Dermatol 2007;57:677-82.)

Port wine stain (PWS) birthmarks or capillary vascular malformations are the most common of all congenital vascular malformations with an incidence of 3 per 1000 live births.[1] They are usually dermatomal and unilateral in distribution but can involve the midline. Any area of the body can be involved. There is an 8% to 15% association with underlying eye and brain abnormalities when PWS involve the facial area.[2] The origin of PWS is unknown. These lesions histologically show ectatic dilatation of normal numbers of capillaries with normal endothelium, in the papillary and mid dermis. One theory of causation is that vascular ectasia results from abnormal neural supply to these capillaries. This has been supported by histologic studies showing decreased numbers of nerve fibers in PWS compared with normal-appearing skin.[3,4] Another suggestion is that a primary abnormality of capillary vessel wall results in ectasia but this remains unconfirmed.[5]

Pure PWS consist of ectatic capillaries of diameters varying from 10 to 150 μm predominantly involving the papillary dermis ranging in depth from 300 to 600 μm.[6,7] Clinically, these range in appearance from pale pink to crimson to purple/blue, with varying degrees of overlying soft-tissue hypertrophy, the latter involving deeper more venulectatic type capillaries. Most are pale pink at birth and can progressively darken and thicken with age. PWS can be associated with significant cosmetic disfigurement and psychologic distress, especially when involving exposed areas such as the face.[8]

Abbreviations used:

IPL:	intense pulsed light
Nd:	neodymium
PDL:	pulsed dye laser
PDT:	photodynamic therapy
PWS:	port wine stain
YAG:	yttrium-aluminum-garnet

TREATMENT OF PWS WITH THE PULSED DYE LASER

Until the early 1980s there was no effective treatment available for PWS apart from cosmetic camouflage concealment. Early lasers such as the continuous wave carbon-dioxide and argon lasers were relatively nonselective and resulted in significant scarring.[9] The introduction of the concept of selective photothermolysis with the 577-nm (and later the longer wavelength 585-nm) pulsed dye laser (PDL) revolutionized PWS treatment.[10] This monochromatic yellow light is selectively absorbed by oxyhemoglobin in the dermal ectatic capillaries (with relatively low melanin absorption at the dermoepidermal junction). Pulsing at 450 microseconds, which is less than the thermal relaxation time of these vessels, confined the heat energy to the

From the Royal Victoria Hospitals[a] and Ulster Hospital.[b]
Funding sources: None.
Conflicts of interest: None declared.
Reprints not available from the authors.
Correspondence to: Zaid F. Jasim, MRCP, Department of Dermatology, Level 5 Outpatients, Royal Victoria Hospitals, Belfast BT12 6BA, United Kingdom. E-mail: zfjasim@hotmail.com.
Published online July 24, 2007.
0190-9622/$32.00

doi:10.1016/j.jaad.2007.01.019

vessels themselves while allowing high peak energy fluences. This allowed selective heating and destruction of the capillary endothelium. This theoretic concept was supported by the evidence from early clinical studies with the PDL. These studies suggested close to 100% lightening could be produced with very little risk of any long-term sequelae such as scarring and pigmentary change.[11]

The resulting introduction of the PDL to clinical practice indeed revolutionized the treatment of PWS. However, it soon became increasingly evident that, although effective, the results of these early studies were overly optimistic. Most studies during the past 20 years show that less than 20% of pure PWS can be lightened completely with the PDL, although 70% will lighten by 50% or more whereas 20% to 30% appear to respond poorly.[12] Certain areas such as the central area of the face and limbs respond less well.[13] Treatment protocols vary but typically would involve 6 to 10 treatments to a given area at 6- to 12-week intervals. Revascularization and recurrence after completion of treatment has also been described to varying degrees.[14] Clinically it is difficult if not impossible to predict which PWS will or will not respond to PDL before initiating treatment. More recently a variety of noninvasive transcutaneous imaging techniques such as laser Doppler imaging, confocal microscopy, photoacoustic probes, and videomicroscopy have been used with varying success to identify dermal morphological vessel characteristics, which may be used to predict treatment response.[4,15]

WHY DO MOST PWS NOT CLEAR COMPLETELY WITH PDL AND SOME NOT LIGHTEN AT ALL?

The reasons for PDL nonresponsiveness are both multiple and complex. PWS are dynamic lesions consisting of multiple ectatic capillaries of varying diameters, endothelial wall thickness, depths, and flow rates containing varying amounts of both oxygenated and deoxygenated hemoglobin depending on whether they are nearer the arterial or venous end of the capillary spectrum. In addition, the overlying epidermis and papillary dermis varies in thickness depending on body site, and melanin content of the dermoepidermal junction varies depending on Fitzpatrick and ethnic skin type. With this in mind it is not surprising that a single fixed wavelength/pulse duration laser system such as the early 585-nm, 0.45-millisecond PDL does not produce optimum results in all PWS marks.

The main mechanism by which the PDL selectively destroys ectatic capillaries in PWS is thought to be by photothermolysis, ie, light converted to heat inside the capillary that results in irreversible damage to the capillary vessel wall. This wall must be destroyed completely if the capillary is not to canalize or regenerate. There are various explanations as to why PDL cannot destroy all the ectatic capillaries within PWS. These include the following.

Inadequate depth of penetration of laser light; deeper dermal capillaries may be inaccessible to PDL light, which only penetrates up to 1 mm into the skin

This might be the cause for nonclearance of PWS in the central face where deeper vessels escape the effect of PDL. In an attempt to remedy this, longer wavelength systems (which penetrate deeper because of decreased optical scattering and epidermal melanin absorption) such as the 595-nm PDL, 755-nm alexandrite, 810-nm diode, and 1064-nm neodymium (Nd):yttrium-aluminum-garnet (YAG) have been developed. These wavelengths have less hemoglobin absorption; thus, higher laser fluences are required to achieve adequate capillary heating, with resulting increase in risk of epidermal and dermal side effects.

Inadequate conduction of laser-induced heating from the centrally situated hemoglobin chromophore to the outer vessel wall in larger diameter capillaries; hence, the vessel wall is not irreversibly damaged, allowing repair and regeneration

The time taken for laser-induced heating to conduct in sufficient quantities to irreversibly damage the capillary endothelial wall is known as thermal damage time. This is significantly longer than thermal relaxation time, classically defined as the time taken for the heat generated in the vessel to diminish by half. Ideal thermal damage times have been shown to vary from 1 to 10 milliseconds in PWS in which capillary diameter typically varies from 20 to 150 μm.[16,17] This is far longer than the 0.45-millisecond pulse duration of early PDL. This has led to the introduction of longer and variable pulse width lasers of varying wavelengths ranging from 1 to 50 milliseconds. Generally speaking, larger diameter capillaries are best treated with longer laser pulse widths at lower fluences, whereas smaller vessels require higher fluence and shorter pulse durations.

Inadequate blood volume; hence, hemoglobin chromophore in small diameter capillaries less than 50 μm in diameter[18]

In vessels of this size the small amount of laser light energy absorbed by the hemoglobin cannot generate enough heat to damage the vessel wall. This is thought to account for treatment failure in flat light-pink PWS. Attempts to remedy this, by

producing vasodilation and slowing of blood flow, in small capillaries before treatment by suction or blood pressure cuff–induced impaired venous return have produced some therapeutic improvement.[19] In a similar way placing the bed in head down (Trendelenburg) position could produce benefit in treatment of facial PWS. Amethocaine, a local anesthetic cream that causes capillary vasodilation, may also theoretically offer some therapeutic benefit when applied before PDL treatment. The potential therapeutic benefit of other topical vasodilatory agents such as glyceryl trinitrate or nifedipine may be worthy of further investigation.

Inadequate fluence entering the capillary limits vessel wall damage

Maximum fluence in early PDL systems was limited because of absorption of yellow light by overlying epidermal melanin, with higher fluences resulting in unacceptable epidermal side effects such as crusting, blistering, pigmentation, and even scarring. The introduction of selective epidermal cooling by a variety of different methods including cold air (forced air convection), cryogen spray, and contact cooling (sapphire window) has generally allowed the use of higher fluences in PDL and other vascular laser systems with resulting increase in capillary damage and therapeutic efficacy.

Mass destruction of papillary dermal capillaries by the short wavelength PDL may cause buildup of visible light impenetrable fibrous tissue in the papillary dermis, preventing laser light at subsequent treatment sessions from penetrating to deeper capillaries.[20]

This could potentially be remedied by initially using longer wavelength more deeply penetrating laser systems such as the 1064-nm Nd:YAG, combined with selective cooling of the epidermis and papillary dermis, to selectively treat deeper capillaries first, followed by later treatment sessions with shorter wavelength less deeply penetrating systems such as the PDL to treat the more superficial vessels.

CURRENT MANAGEMENT OF PDL-RESISTANT PWS

Currently the PDL is still the gold standard for treatment of PWS because of its proven clinical efficacy and excellent safety profile. Most PWS will initially be treated for 6 to 8 sessions with this laser. Treatment early in life requires fewer sessions[11] and might improve outcome. The laser used most commonly in clinical practice is the 595-nm PDL with variable pulse width (range 0.45-40 milliseconds; usually 0.45-1.5 milliseconds is used) in combination with selective epidermal cooling by cryogen spray, cold air, contact, or cool gel compresses. This is thought to be more efficacious than the older 585-nm, 0.45-millisecond pulse width PDL for a variety of reasons. These include longer wavelength and larger spot sizes with deeper penetration, selective epidermal cooling that allows use of higher fluences, and use of longer pulse widths that can be adjusted to correspond to capillary thermal damage time.[21] Clinical end points for PDL treatment include complete lightening (<25% of cases) or, most commonly, failure to lighten any further with subsequent treatment. Most vascular laser centers have a large number of patients whose PWS have achieved significant lightening with the PDL but whose marks are still very noticeable, with a small number (approximately 20%) whose marks do not lighten at all. What currently are practical options for such patients? These may include the following.

Further treatment with the PDL using longer pulse durations ranging from 2 to 40 milliseconds that, in theory, may treat larger diameter capillaries resistant to treatment at shorter pulse durations

Similarly, treatment with higher-powered PDL using larger spot sizes should reach deeper capillaries not previously accessible with less powerful lasers with smaller spot size. However, clinical studies and experience using both approaches either alone or in combination have shown only little further therapeutic benefit.[22]

Further treatment with PDL at lower subpurpuric fluences (6-7 mJ/cm^{-2}) with no immediate or transiently appearing but rapidly fading purpura, usually combined with slightly longer pulse durations ranging from 3 to 6 milliseconds

Using pulse stacking (2-3 consecutive pulses applied immediately after the preceding pulse to the same spot[23]) may produce further lightening of PWS. The theory is that cumulative gentle heating may produce overall greater capillary heating and, hence, more efficient capillary wall damage than that achievable by a single high-energy short duration purpura-inducing pulse of laser light. This is because the thermal relaxation time of the epidermis (approximately 1 millisecond) is shorter than that of dermal capillaries. Hence, pulse stacking delivers cumulative heating to dermal capillaries while allowing the epidermis to cool completely between pulses while the amount of laser energy delivered to the capillary wall in a single pulse high fluence short pulse is limited to a greater extent by risk of epidermal damage. PDL pulse stacking might be expected

to be of most benefit for flat pink PDL-resistant PWS with small diameter (10-50 μm) vessels in which single short pulse high fluence PDL is relatively ineffective. Lower fluence should be used for treating areas prone to scarring (eg, PWS of the neck).

For pink flat PDL-resistant PWS, treatment with an intense pulsed light (IPL) device might also be of benefit. IPL devices emit polychromatic noncoherent light (wavelength spectrum from 500-1200 nm). Various filters can be used (eg, 500 and 550 nm) that filter out light below the indicated wavelength, mainly dependant on skin color. IPL can be single or multipulsed with varying delays between pulses. Multiple pulses are particularly useful to allow epidermal sparing and greater cumulative heating in the dermal capillaries in a manner similar to pulse stacking already described with the PDL. In addition, most second- and third-generation IPL devices incorporate a contact epidermal cooling system. Theoretically, therefore, IPL treatment with a wider spectrum of wavelengths, with high fluences, and greater cumulative capillary heating with the multipulse mode may result in further destruction of residual variable diameter and deeper ectatic dermal capillaries with resultant further PWS lightening. There is some clinical evidence to support this with one study showing that 50% of PDL-resistant PWS could be lightened by up to 50% with subsequent IPL treatment.[24] As clinical prediction of lightening is impossible, test treatments are advisable before embarking on this treatment course as IPL at high energy does have a significantly less favorable side-effect profile than PDL.

Other options for pink flat PDL-resistant PWS include the variable pulse width frequency doubled 532-nm Nd:YAG or KTP lasers, which can occasionally produce further lightening.[22] These short wavelength lasers penetrate less deeply than the PDL and have a significantly poorer side-effect profile because of high epidermal melanin absorption at this wavelength despite epidermal cooling.

For PDL-resistant PWS with a purple or blue tinge, with or without thicker overlying skin and/or nodularity (because of persisting deeper and wider diameter capillaries), treatment with a more deeply penetrating, longer variable pulse width lasers such as the millisecond pulsed 1064-nm Nd:YAG has been shown to be beneficial.[25,26] The 810-nm diode or the 755-nm alexandrite are less effective alternatives.

In practice, the spot size (usually 5-12 mm) and pulse duration (usually 10-20 milliseconds) are selected to correspond to the surface area of the lesion, maximize depth of penetration, and correspond to perceived capillary diameter (usually 100-150 μm). Initially, relatively low subpurpuric fluence is chosen increasing the fluence until persistent purpura (the desired clinical end point) is achieved. Because high fluences are required, selective epidermal cooling is mandatory. Despite this, the side-effect profile of these lasers is not as good as that of the PDL, as they have a much higher risk of scarring. Significant operator expertise is, hence, a necessary prerequisite and test treatments to assess efficacy before treatment of larger areas are recommended. On the positive side, pigmentary change is much less common than with the PDL because of low melanin absorption at these longer wavelengths with the added benefit of being able to treat darker skin types. The role of these deeper penetrating lasers in treatment of PWS with hypertrophy, such as the lip area, needs further investigation.

Despite all the measures described above, further significant lightening in the vast majority of PDL-resistant PWS in clinical practice is often minimal with significant cosmetic disfigurement persisting despite the clinician's best efforts. In such cases other measures such as cosmetic camouflage makeup and or surgical excision or reduction should also be considered.

WHAT DOES THE FUTURE HOLD?

The pathogenesis and genetics of PWS are worthy of further study. New improved molecular genetic techniques such as complementary DNA microarray analysis can synchronously survey multiple gene functions and may help shed further light on the origin of these lesions. Specifically, possible abnormalities in dermal capillary endothelial cells and autonomic neurons associated with these should be investigated. The aim would be prenatal diagnosis, especially of PWS-associated syndromes and more complex vascular malformations, definitive therapeutic intervention, or even prevention.

The development of improved, more clinically applicable and affordable noninvasive transcutaneous imaging systems may further our understanding of the morphology, physiology, and dynamics of PWS. Ideally such systems could be used to better elucidate the complex morphological characteristics of individual PWS with a view to formulating more logical therapeutic approaches with different types of modalities including laser, IPL, and electrosurgery. Pretreatment prediction of therapeutic outcome could also become possible based on individual PWS characteristics. Ultimately such systems could also allow design of improved laser and other treatment systems.

New combined modality laser systems such as the Cynergy Multiplex (Cynosure Inc, Westford, Mass) laser system (PDL + Nd:YAG), which can deliver

pulsed sequential 595-nm followed by 1064-nm light some 50 to 2000 milliseconds later, are an interesting development. The rationale is that the initial pulse of subpurpuric 595-nm light causes formation of methemoglobin within the capillary. As methemoglobin has a significant absorption peak around 1064 nm, this increases intracapillary absorption of the subsequently administered 1064-nm pulse. The use of this multiplex 595-/1064-nm laser treatment has been shown to result in a greater depth vascular coagulation and safe and effective treatment of recalcitrant vascular lesions.[27,28]

Photodynamic therapy (PDT) is a new therapeutic modality that shows promise in treatment of PWS. This involves either transcutaneous or intracirculatory addition of an exogenous chromophore into the ectatic capillaries. Chromophores used have mostly included porphyrin precursors, such as hepatoporphyrin, benzoporphyrin (both administered intravenously), and aminolavulinic acid, which is topically adminstered.[29-32] Porphyrins have a wide spectrum of absorption with at least 4 significant peaks in the visible light range. These include large peaks in the blue and red and a smaller peak in the yellow range. Capillaries containing porphyrin derivatives and oxygen can be selectively irradiated with either coherent (laser) or noncoherent light of the appropriate wavelength. This generates a simultaneous intracapillary photothermal and photochemical reaction, with both direct capillary wall heating and indirect damage by production of protoporphyrin IX and oxygen-derived free radicals. Capillary destruction is, hence, theoretically more efficient than with PDL alone (photothermal only). In theory, therefore, PDT may be prove more efficient in terms of greater lightening and less treatment sessions than PDL alone. Most importantly, PDT could show therapeutic benefit in pale-pink PWS with capillaries ranging in diameter from 10 to 50 μm in which standard PDL is relatively ineffective. PDT using PDL light has indeed been shown in one study to have lightening effect on PWS.[33] However, currently practical problems with PDT limit its clinical application. These include high cost in physician time, drugs, and equipment; inefficient transcutaneous absorption of aminolevulinic acid into dermal capillaries; and prolonged systemic visible light sensitivity after administration of intravenous porphyrin derivatives.

The new concept of electrical light optical synergy technology may also have therapeutic benefits in treatment of PWS. This transcutaneous technology combines either a monopolar or bipolar radiofrequency device with either laser or IPL. An initial low fluence laser/IPL pulse of appropriate wavelength selectively heats the intracapillary hemoglobin chromophore. This heating lowers impedance of the hemoglobin to electrical current. Thus, electrical current applied in a pulsed manner immediately after laser/IPL passes more readily through the heated dermal capillary resulting in selective heating with relative sparing of other surrounding structures. In theory, electrical heating induced in this way may destroy capillaries in PWS more effectively than laser/IPL heating. To date most studies using electrical light optical synergy have been in the field of hair removal and photorejuvenation.[34] The potential for electrical light optical synergy in treatment of PWS is worthy of further research.

The main limitation of transcutaneous laser in treatment of PWS is that light with the greatest hemoglobin absorption is relatively short wavelength 484/515 nm (blue green) and 577/585 nm (yellow). These short wavelengths penetrate the skin to depths of less than 1 mm mainly as a result of high optical scatter and high level of melanin absorption at the dermoepidermal junction. In addition, high melanin absorption at these wavelengths limits the fluences used as a result of unacceptable levels of epidermal heating (despite selective epidermal cooling) with resultant side effects such as crusting, blistering, and pigmentary change. Both of these factors could be improved by removal of the epidermis before pulsed delivery of laser light. This would remove the vast majority of melanocytes at the dermoepidermal junction and at least 100 μm of tissue between the laser and the target dermal capillaries, effectively allowing increased depth of penetration, and use of higher more therapeutic fluences. Temporary epidermal removal followed by complete regeneration without scarring within 5 to 7 days is easily achievable with the short-pulse 2094-nm erbium:YAG laser. This laser is absorbed almost exclusively by water and causes vaporization with almost no underlying tissue heating. The depth of vaporization is determined by the fluence setting and number of passes, with relatively easily defined clinical end points. In theory, erbium laser epidermal removal immediately before pulsed 577-/585-/595-nm PDL or shorter wavelength 532-nm Nd:YAG/KTP YAG could be more effective than PDL alone. This is an area that warrants further study.

Similarly, optical clearing agents that improve the depth of laser light by reducing tissue scattering may allow use of more efficient shorter wavelength lasers and improve existing PDL efficacy. Hyperosmotic agents, such as glycerol, have been shown to reduce scattering in skin.[35] Two main theories have been suggested. First, the index of refraction of the tissue constituents (such as collagen and cells) could be more closely matched by the agent than the interstitial or

intercellular fluids. The second theory is that dehydration of the cells as a result of the hyperosmotic agent causes the tissue to become more densely packed.

Ultimately, further study of the pathogenesis and genetics of PWS will provide the answers as to the origin of these relatively common and disfiguring lesions. This should allow, in the short to medium term, prenatal diagnosis. This is especially important in PWS-associated syndromes and more complex vascular malformations, and in the longer-term definitive curative treatment and even prevention.

REFERENCES

1. Alper JC, Holmes LB. The incidence and significance of birthmarks in a cohort of 4641 newborns. Pediatr Dermatol 1983;1:58-68.
2. Enjolras O, Riche MC, Merland JJ. Facial port wine stains and Sturge-Weber syndrome. Pediatrics 1985;76:48-51.
3. Smoller BR, Rosen S. Port wine stains: a disease of altered neural modulation of blood vessels? Arch Dermatol 1986; 122:177-9.
4. Selim MM, Kelly KM, Nelson JS, Wendelschafer-Crabb G, Kennedy WR, Zelickson BD. Confocal microscopy study of nerves and blood vessels in untreated and treated port wine stains: preliminary observations. Dermatol Surg 2004;30:892-7.
5. Finley JL, Clarke RA, Colvin RB, Blackman R, Noe J, Rosen S. Immunofluorescent staining with antibodies to factor VIII, fibronectin, and collagenous basement membrane protein in normal human skin and port wine stains. Arch Dermatol 1982;118:971-5.
6. Viator JA, Au G, Paltauf G, Jacques SL, Prahl SA, Ren H, et al. Clinical testing of a photoacoustic probe for port wine stain depth determination. Lasers Surg Med 2002;30:141-8.
7. Shafirstein G, Bäumler W, Lapidoth M, Ferguson S, North PE, Waner M. A new mathematical approach to the diffusion approximation theory for selective photothermolysis modelling and its implication in laser treatment of port-wine stains. Lasers Surg Med 2004;34:335-47.
8. Troilius A, Wrangsjo B, Ljunggren B. Potential psychological benefits from early treatment of port-wine stains in children. Br J Dermatol 1998;139:59-65.
9. Olbricht SM, Stern RS, Tang SV, Noe JM, Arndt KA. Complications of cutaneous laser surgery: a survey. Arch Dermatol 1987; 123:345-9.
10. Anderson RR, Parrish JA. Selective photothermolysis: precise microsurgery by selective absorption of pulsed radiation. Science 1983;220:524-7.
11. Tan OT, Sherwood K, Gilchrest BA. Treatment of children with port-wine stains using the flashlamp-pulsed tunable dye laser. N Engl J Med 1989;320:416-21.
12. Woo WK, Handley JM. Does fluence matter in the laser treatment of port-wine stains? Clin Exp Dermatol 2003;28:556-7.
13. Renfro L, Geronemus RG. Anatomical differences of port wine stains in response to treatment with the pulsed dye laser. Arch Dermatol 1993;129:182-8.
14. Orten SS, Waner M, Flock S, Roberson PK, Kincannon J. Port wine stains: an assessment of five years of treatment. Arch Otolaryngol Head Neck Surg 1996;122:1174-9.
15. Sevila A, Nagore E, Botella-Estrada R, Sanmartin O, Requena C, Serra-Guillen C, et al. Videomicroscopy of venular malformations (port wine stain type): prediction of response to pulsed dye laser. Pediatr Dermatol 2004;21:589-96.
16. Altschuler GB, Anderson RR, Manstein D, Zenzie HH, Smirnov MZ. Extended theory of selective photothermolysis. Lasers Surg Med 2001;29:416-32.
17. Dover JS. New approaches to laser treatment of vascular lesions. Australas J Dermatol 2000;41:14-8.
18. Kono T, Groff WF, Sakurai H. Treatment of port wine stains with the pulse dye laser. Ann Plast Surg 2006;56:460-3.
19. Svaasland LO, Aguilar G, Viator JA, Randeberg LL, Kimel S, Nelson JS. Increase of dermal blood volume fraction reduces the threshold for laser-induced purpura: implications for port wine stain laser treatment. Lasers Surg Med 2004;34: 182-8.
20. Lanigan SW. Port wine stains unresponsive to pulsed dye laser: explanations and solutions. Br J Dermatol 1998;139: 173-7.
21. Laube S, Taibjee S, Lanigan SW. Treatment of resistant port wine stains with the V beam pulsed dye laser. Lasers Surg Med 2003;33:282-7.
22. Woo WK, Jasim ZF, Handley JM. Evaluating the efficacy of treatment of resistant port-wine stains with variable-pulse 595-nm pulsed dye and 532-nm Nd:YAG lasers. Dermatol Surg 2004;30:158-62.
23. Rohrer TE, Chatrath V, Iyengar V. Does pulse stacking improve the results of treatment with variable-pulse pulsed-dye lasers? Dermatol Surg 2004;30:163-7.
24. Bjerring P, Christiansen K, Troilius A. Intense pulsed light source for the treatment of dye laser resistant port wine stains. J Cosmet Laser Ther 2003;5:7-13.
25. Groot D, Rao J, Johnston P, Nakatsui T. Algorithm for using a long-pulsed Nd:Yag laser in the treatment of deep cutaneous vascular lesions. Dermatol Surg 2003;29:35-42.
26. Yang MU, Yaroslavsky AN, Farinelli WA, Flotte TJ, Rius-Diaz F, Tsao SS, et al. Long-pulsed neodymium:yttrium-aluminum-garnet laser treatment for port-wine stains. J Am Acad Dermatol 2005;52:480-90.
27. Chapas A, Fazeli A, Goldberg D, Geronimus R. Sequential, dual wavelength treatment of port wine birthmarks: pilot study [abstract]. Lasers Surg Med 2006;Suppl 18:21.
28. Tanghetti EA. Multiplex 595 nm, 1064 nm laser treatment for blebbed port wine birthmarks and telangiectasia [abstract]. Lasers Surg Med 2006;Suppl 18:21.
29. Evans AV, Robson A, Barlow RJ, Kurwa HA. Treatment of port wine stains with photodynamic therapy using pulsed dye laser as a light source compared with pulsed dye laser alone: a pilot study. Lasers Surg Med 2005;36:266-9.
30. Kelly KM, Kimel S, Smith T, Stacy A, Hammer-Wilson MJ, Svaasand LO, et al. Combined photodynamic and photothermal-induced injury enhances damage to in vivo model blood vessels. Lasers Surg Med 2004;34:407-13.
31. Jiang L, Gu Y, Li X, Zhao X, Li J, Wang K, et al. Changes of skin perfusion after photodynamic therapy for port wine stain. Chin Med J (Engl) 1998;111:136-8.
32. Lin XX, Wang W, Wu SF, Yang C, Chang TS. Treatment of capillary vascular malformation (port wine staina) with photochemotherapy. Plast Reconstr Surg 1997;99:1826-30.
33. Tournas JA, Choi B, Kelly KM. Combined photodynamic and pulsed dye laser treatment of port wine stains [abstract]. Lasers Surg Med 2006;Suppl 18:30.
34. Sadick NS, Laughlin SA. Effective epilation of white and blond hair using combined radiofrequency and optical energy. J Cosmet Laser Ther 2004;6:27-31.
35. Vargas G, Readinger A, Dozier SS, Welch AJ. Morphological changes in blood vessels produced by hyperosmotic agents and measured by optical coherence tomography. Photochem Photobiol 2003;77:541-9.