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Port-Wine Stain Laser Treatments and Novel Approaches

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Abstract

Background and Objectives Port-wine stains (PWSs) are capillary vascular malformations that are commonly resistant to treatment. Currently, the pulsed dye laser (PDL) is the treatment of choice. Multiple treatments are required and complete blanching after laser irradiation is rarely achieved. We review current therapeutic modalities for PWSs and recent developments for enhanced clearance.

Study Design/Materials and Methods Relevant literature was reviewed including PDL modifications for improved efficacy, alternative laser devices for treatment-resistant PWSs, and the addition of agents to modulate the wound-healing response after laser irradiation.

Results Although PDL is the treatment of choice for PWSs, increased understanding of interactions between PWSs and PDL has led to improvements in therapeutic outcome in terms of lesion blanching.

Conclusions Preliminary evidence of combination therapy using antiangiogenic agents after laser irradiation appears promising and could lead to the development of a new standard of care for PWSs.

Keywords
- port-wine stains
- capillary malformation
- laser
- selective photothermolysis
- pulsed dye laser

Port-wine stains (PWSs), also referred to as "nevus flammeus," are cutaneous vascular malformations involving the postcapillary venules with potentially devastating physical and psychological complications.[1] PWSs appear as pink-red to violaceous patches on the skin. PWS occurs in an estimated 3 children per 1,000 live births, affecting males and females and all racial groups equally. Approximately 900,000 individuals in the United States and 20 million people worldwide have PWS birthmarks. There appears to be no hereditary predilection for PWS within families. There are no known risk factors for PWSs and no known ways to prevent them. PWSs may also be acquired secondary to trauma in rare cases.[2,3]

Although PWSs may be localized or segmental anywhere on the body, most PWSs involve the head and neck region, classically following the trigeminal nerve distribution on the face. The cause and origin of PWS remain incompletely understood. The most likely hypothesis for the development of PWS is the deficiency or absence of surrounding neurons regulating blood flow through the ectatic postcapillary venules. As a result, the blood vessels are unable to constrict normally and remain permanently dilated. It is believed that PWSs develop within the first 2 to 8 weeks of gestation.[4]

PWSs are part of a constellation of disorders known as "vascular malformations" and may be one of a group of symptoms or signs, perhaps as part of a larger disorder or syndrome such as Sturge-Weber syndrome (SWS; encephalotrigeminal angiomatosis), Klippel-Trenaunay syndrome, Cobb syndrome, and Proteus syndrome (PS). Thus, it is important that physicians evaluating patients with PWS recognize that associated medical problems may be present.

One important example is SWS (►**Fig. 1**), which is a sporadic neurological disorder that consists of a PWS usually in the trigeminal V1 distribution in association with ipsilateral ocular and leptomeningeal anomalies.[5] Infants with

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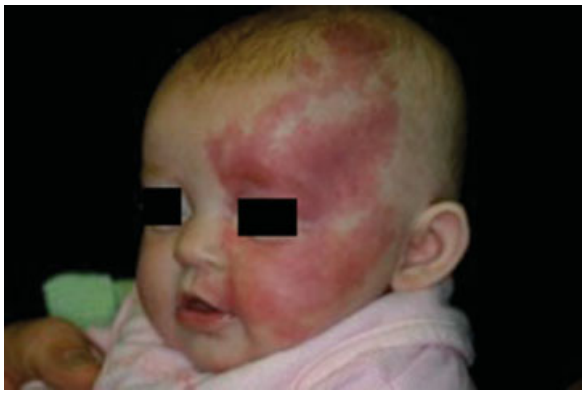

Figure 1 A patient with Sturge-Weber syndrome with a port-wine stain in the V1/V2/V3 distribution.

bilateral PWS have a higher risk of SWS and have a worse prognosis.[6] Ocular involvement may present at birth as congenital glaucoma. However, intraocular pressure more commonly increases over time. Thus, it is important for these patients to have periodic ocular exams and measurement of eye pressures. Neurological complications present as seizures and are due to the presence of capillary malformations within the pia mater on the ipsilateral side of the PWS. Seizures are often recalcitrant to anticonvulsants. Neurological evaluation with CT with iodinated contrast and MRI with gadolinium enhancement is considered mandatory in infants with a PWS in the V1 distribution. The pathogenesis of SWS is still not fully understood.

Klippel-Trenaunay syndrome (►**Fig. 2**) is a capillary-venous malformation or capillary-lymphatic-venous malformation of the limb, which leads to progressive overgrowth and deformity of the affected limb. The skin may have the appearance of a haphazardly distributed blotchy, capillary stain, or a more geographic stain that presents at birth. Geographic stains have a worse prognosis in regards to limb hypertrophy and associated complications, such as thromboses. Evaluation may be done with ultrasonography, Doppler ultrasonography, MRI, and sometimes lymphoscintigraphy.

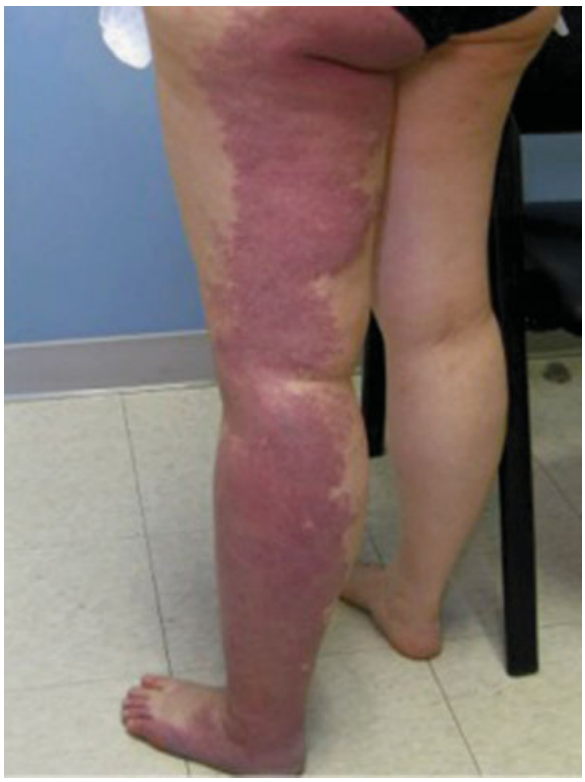

Figure 2 A patient with Klippel-Trenaunay syndrome with a port-wine stain on the leg and associated soft tissue hypertrophy of the affected limb.

PS is characterized by the overgrowth in a variety of tissues such as the skin, connective tissue, and brain. New evidence shows that PS is caused by a somatic activating mutation in the oncogene, AKT1.[7] This supports the hypothesis that the syndrome is caused by somatic mosaicism, which is lethal when constitutive.[8] Common features of PS include vascular malformations (especially PWSs), epidermal nevi, localized macrosomia, limb gigantism, dermal hypoplasia, cerebriform palmar or plantar hyperplasia, choristomas of the eye, visceral hamartomas, and abnormal fat deposition.

Capillary malformations may also present in combination with melanocytic or epidermal nevi as a manifestation of genetic twin spotting, classified as types of phakomatosis pigmentovascularis (PPV). There are four types of PPV. Type I represents a capillary malformation in association with an epidermal nevus. Type II represents a capillary malformation in association with dermal melanocytosis and sometimes a nevus anemicus. Type III includes a capillary malformation with a nevus spilus and occasionally a nevus anemicus. Last, type IV is comprised of a capillary malformation, dermal melanocytosis, nevus spilus, and sometimes a nevus anemicus. In conclusion, it is not uncommon to see a PWS overlying an arteriovenous malformation, arterial malformation, venous malformation, or lymphatic malformation and, therefore, the surgeon should look beyond the skin for any underlying problem.

PWS is a *progressive* vascular malformation of the skin; unlike hemangiomas, PWSs do not have a tendency to involute. PWSs are well demarcated and flat and grow proportionately in surface area with the child. In infants and young children, PWSs are flat red macules. However, the lesions tend to darken progressively to purple, and by adult age, they often become raised as a result of the development of vascular papules or nodules ("cobblestone formation"). These changes in color and contour are attributed to progressive ectasia of the abnormal dermal vascular plexus. Over time, as the blood vessels become more dilated, they become more susceptible to spontaneous bleeding or hemorrhage following minor trauma. Bleeding can be difficult to control, necessitate hospitalization, and may also increase the likelihood of skin infection. The hypertrophy (increased tissue mass) of underlying soft tissue that occurs in approximately two-thirds of lesions further disfigures the facial features of many patients. For all of the above reasons, most medical specialists agree that it is essential to begin treatment of PWS as early as possible and to maintain treatment to prevent the development of vascular nodules and hypertrophy in later years.

Treatment of PWS

In the past, therapeutic modalities for PWS treatment included excision with skin grafting,[9] cryotherapy, ionizing

radiation, dermabrasion, electrotherapy, or tattooing.[10] All of these have met with limited success and often left cosmetically unacceptable secondary scarring. These are no longer considered viable treatment options. The lesion may be masked by an opaque makeup. However, once the patient's PWS has developed vascular papules or nodules, corrective makeup becomes far less effective.

First Approaches to PWS Laser Treatment

The introduction of the argon laser in the early 1970s represented the first major advance in therapy for PWS.[11] The argon laser produces blue-green light (488 and 514 nm) that is preferentially absorbed by hemoglobin within the PWS blood vessels. The radiant energy absorbed by the vessels is converted to heat, causing thrombosis and destruction of the PWS blood vessels. Unfortunately, the epidermis is not totally spared (due to undesired absorption therein by melanin and other dermal components) and suffers some irreversible damage. Furthermore, the first-generation argon lasers used more medical intervention, and the shortest available pulse duration was 0.01 seconds, thereby contributing to nonspecific thermal damage. For many lesions, the threshold for permanent epidermal damage following argon laser therapy was very close to the threshold for blanching of the PWS. Although the treatment of PWS with the argon laser could produce favorable results, scarring remained a worrisome complication even in the hands of the most skillful practitioner. Scarring was particularly likely in the population of patients expected to gain the most benefit from PWS laser therapy—infants and young children—owing to the propensity for scar formation in younger age groups, particularly on the lips and perialar regions, similar to that seen in children following thermal burn injury. Argon laser therapy is therefore not recommended for PWS in infants and young children. Similar results were reported with other continuous and quasi-continuous lasers such as the copper vapor, krypton ion, argon-pumped dye, and carbon dioxide lasers. Therefore, these lasers are no longer standard of care for PWS therapy.

Selective Photothermolysis of PWS Blood Vessels

Unsatisfactory treatment by nonselective lasers, which resulted in extensive collateral damage, created a demand for a laser capable of more selective destruction of PWS blood vessels. The laser has many inherent properties that contribute to its ability to affect a specific biological outcome. Most important, from a clinical point of view, are the properties of emitted wavelength and pulse duration. If the clinical objective is to cause selective destruction of a specific chromophore, the wavelength chosen should match the highest absorption of the targeted chromophore relative to other optically absorbing molecules.

Given that one goal of treatment is the precise control of thermal energy, the pulse duration of laser irradiation is just as important as optical and tissue factors.[12] One way to maximize the spatial confinement of heat is to use a laser with a pulse duration on the order of the thermal relaxation time (T_r) of the target chromophore. T_r is defined as the time required for the heat generated by the absorbed light energy within the chromophore to cool to one half of the original temperature immediately after the laser pulse. During a lengthy laser exposure, most of the heat produced diffuses away despite its origin in the target structure. The target does not become appreciably warmer than its surroundings because the absorbed energy is invested almost uniformly in heating of the tissue during exposure. As a result, longer pulse durations offer a more generalized heating and, therefore, less spatial selectivity resulting in nonspecific thermal damage to adjacent structures regardless of how carefully one has chosen a wavelength. However, if the laser pulse is suitably brief, its energy is invested in the target chromophore before much heat is lost by thermal diffusion out of the exposure field. A transient maximum temperature differential between the target and adjacent structures is then achieved. Shorter pulse durations confine the laser energy to progressively smaller targets with more spatial selectivity.[12]

The transition from specific to nonspecific thermal damage occurs as the laser exposure equals and then exceeds T_r. Therefore, selective target damage depends on delivering a pulse of light of shorter duration than T_r, which can be estimated because the latter is directly proportional to the square of the diameter of the target and inversely proportional to the thermal diffusivity of the tissue. A laser emitting at a selectively absorbed wavelength with a pulse duration less than T_r can be expected to cause highly selective target damage. This process, termed "selective photothermolysis," was introduced in 1983 by Anderson and Parrish[13] as a means of achieving target chromophore destruction by careful selection of wavelength and pulse duration. Moreover, this was the first of many modeling constructs around which medical lasers would subsequently be manufactured.

Pulsed Dye Laser Treatment

Selective photothermolysis of PWS blood vessels was first achieved by the development of the pulsed dye laser (PDL). First-generation PDLs (577 nm or 585 nm, 0.45 milliseconds) selectively induced photocoagulation of targeted blood vessels in PWS without overlying epidermal damage and with a low incidence of side effects.[14,15] Yellow light produced by the PDL is preferentially absorbed by hemoglobin (a major chromophore in blood) in the PWS blood vessels where, after being converted to heat, it causes thermal damage and thrombosis. Furthermore, because the T_r for cutaneous blood vessels 50 to 150 μm in diameter is between 1.4 to 12.8 milliseconds, the 0.45 to 50 milliseconds pulse duration produced by these lasers matches the T_r for dermal blood vessels thus confining the laser energy to the targeted vessel before much heat is lost by thermal diffusion out of the exposure field.[16]

Histological studies document extensive PDL-induced vascular wall necrosis with subsequent extravasation of red blood cells into the adjacent dermis.[17] Coagulation of intraluminal blood seems to be an intermediate step to destruction of the vessel wall. As laser energy is deposited in the intraluminal blood due to selective absorption of hemoglobin, the heat then diffuses to the vessel wall. Dermal collagen replaces the coagulated blood and vascular wall components leading

to blanching of the PWS. Alternatively, vessel wall rupture may occur in response to explosive vaporization of blood from improper laser parameters. Vessel wall rupture is associated with poor clinical outcomes.[15,18] In these cases, tissue repair mechanisms resolve the purpura and revascularize the PWS lesion with a minimal blanching response.

Increased understanding of the interaction between lasers and PWS has led to improvement in PDL devices. Second-generation PDL technology incorporates the use of larger spot sizes, higher energy densities, varying pulse durations, and dynamic cooling for more effective treatment of PWS via greater vessel heating and deeper vascular injury. The improved technology, which allows the user to specify pulse duration, targets the heterogeneity in blood vessel sizes that are characteristic of PWSs.[19,20]

Epidermal injury from melanin absorption of PDL energy is prevented by active cooling of the skin surface prior to irradiation. Varying the cooling time, termed "dynamic cooling," controls the extent of cooling. Different cooling devices including liquid cryogen sprays,[21] contact cooling, and chilled air cooling[22] are currently available. However, contact and chilled air cooling inevitably result in nonselective ("bulk") cooling of the entire skin, which results in reduction in temperature of the targeted blood vessels offsetting the benefit of these cooling techniques for PWS laser therapy. Therefore, PDL with dynamic epidermal cooling by liquid cryogen sprays is currently the treatment of choice for PWSs.[21,23] Cryogen spray cooling uses tetrafluoroethane, which has a low boiling temperature (−26.2°C) and a relatively high latent heat of vaporization (198 kJ/kg at 0°C), to extract heat from the skin surface by rapid evaporation, which results in the cooling being confined to the epidermis.[21,23] A further important advantage of cryogen spray cooling is the ability to electronically control the timing of the spurt, which offers a predictable cooling effect and reliable safety margin with respect to undesirable thermal injury.

PDL treatments are administered by moving the laser handpiece across the PWS in a systematic fashion to deliver a series of pulses using a 7- to 12-mm spot size. Complete blanching of the lesion is rarely achieved in one treatment. More commonly, several treatment sessions spaced at 4- to 8-week intervals are required for maximum efficacy. The number of treatments is variable and unpredictable.[24]

Treatment side effects are mainly limited to postoperative edema, erythematous flare, and purpura. Edema and erythema generally resolve within 48 hours whereas purpura, the temporary purple discoloration or "bruising effect" induced by PDL treatment of PWS, generally resolves within 2 weeks. The light-induced reduction in the dermal blood volume fraction is observed clinically as PWS lesion blanching.

Dyspigmentation may occur in darker skin phototypes, but is usually resolved within 6 to 12 months. With the addition of epidermal cooling, most notably cryogen spray cooling, the risk of dyspigmentation and scarring is largely avoided.

PWS Blood Vessel Heterogeneity

The blood vessel heterogeneity of each individual PWS makes it difficult to define an ideal radiant exposure and pulse duration to achieve maximum lesion fading.[25] Advances in PDL technology, such as the ability to adjust pulse durations, the use of larger spot sizes with higher radiant exposures, and dynamic cooling, addresses PWS heterogeneity and allows for greater vessel heating and deeper vascular injury.[21] The heterogeneity of the vasculature is compounded by variation in optical characteristics between different patients and between different anatomical locations on the same patient. For example, central face (particularly those lesions involving the V2 dermatome) PWSs respond less effectively to treatment as compared with other areas of the lateral face and neck.[26] PWSs involving areas over bony prominences respond well to laser therapy. Upper body PWSs respond better to laser therapy than those lesions on the lower body and extremities. PWS lesions associated with SWS or Klippel-Trenaunay syndrome respond poorly to laser therapy. Thus, any study evaluating the effectiveness of laser treatment needs to account for PWS anatomic variation of the response to treatment.

Commonly, several devices are used during an extended treatment protocol to destroy vessels of different sizes. When therapy is first initiated, shorter wavelengths and pulses are used to target the typical small (30 to 50 μm) diameter vessels seen in pediatric PWSs. Thereafter, longer wavelengths and pulses can be used to target the residual larger and deeper PWS blood vessels. This approach produces reasonably good blanching in most PWS lesions.

When patients are referred to our institution after treatments at other centers, all previous medical records are reviewed to determine the laser device that was used. Changing the wavelength or pulse duration of the laser can result in substantial PWS fading not previously observed with single device therapy.

Early Treatment of Pediatric PWS

Early treatment of an infant's PWS is an important consideration. Aggressive treatment of infants and young children is well tolerated and improves PWS clearance.[27] It has been demonstrated that the most successful outcomes are seen in patients less than 1 year old with PWS smaller than 20 cm^2.[28] PWSs are smaller during infancy because they maintain their relative size with growth and clearance of the lesions more easily facilitated. Given that blood vessel diameter (30 to 300 μm), depth distribution (100 to 1000 μm), epidermal thickness (50 to 150 μm), and melanin concentration vary among patients,[29,30] there are many optical advantages to treating patients earlier in life. First, there is less epidermal melanin to compete for laser light absorption. Second, younger patients have less dermal collagen, which decreases the amount of light backscattered out of the skin. Last, the thinner dermis and lower fractional blood volume found in younger patients allows more light to penetrate the skin, assisting destruction of targeted PWS blood vessels. Beyond optical advantages, it is easier to immobilize infants during the uncomfortable procedure than more resistant toddlers.

Another consideration for early treatment of a PWS is the prevention of the development of hypertrophic lesions. It has been made evident that treatment of a PWS in its earlier

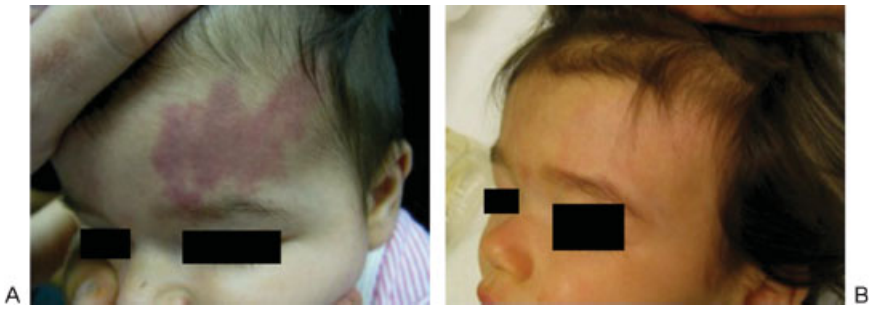

Figure 3 (A) A port-wine stain on the face of a pediatric patient. (B) Excellent response after five treatments with a pulsed dye (595 nm) laser.

macular stage will prevent the development of a more hypertrophic component. Biopsies done after laser treatment of a PWS show smaller and fewer blood vessels compared with pretreatment biopsies.[31] Therefore, there is less opportunity for progression of the vessels to a more ectatic state. Thus, PWSs should be treated as soon as possible for optimal clearance and prevention of thicker, more difficult to treat, lesions (►**Fig. 3**).

Summary of Current Status of PDL Treatment of PWS

In summary, the PDL produces reasonably good results in terms of PWS lesion blanching in most patients with PWS (►**Fig. 4**). However, if the ultimate standard required is complete blanching of the lesion, the average success rate is below 20%.[24] PWS response remains to a certain degree variable and unpredictable with many patients' PWS fading minimally. However, the benefits of laser therapy far outweigh the risks of no treatment and should be considered a medical necessity. If left untreated, many PWSs often become incompatible with normal life due to the development of vascular nodules on the skin surface, which can often bleed spontaneously with incidental trauma. It has become clear that treatment of a PWS in its macular stage will prevent the development of the hypertrophic component of the lesion. Thus, the opportunity for progression of these lesions to a more ectatic state is less likely to occur. Although the majority of PWS lesions do not recur, some lesional redarkening many years later has been reported after successful PDL therapy. One possible explanation might be continuous dilatation of the remaining ectatic vessels, which also lack autonomic innervation. Patients who do experience some redarkening will usually only require one or two treatments to return to their former level of PWS blanching.

New Approaches to PWS Laser Treatment

Multiple Cryogen Spurts with Multiple Laser Pulses

Presently, all patients are treated using a single cryogen spurt (SCS; for epidermal protection) and single laser pulse exposure (SLP). Due to the strong superficial light absorption by hemoglobin, large PWS vessels (> 150 µm diameter) can only be partially coagulated because blood in the center of the vessel is inadequately heated, which explains why current SCS-SLP treatment results in a poor therapeutic outcome in PWS lesions featuring large vessels. A histological study using confocal microscopy confirmed that mean PWS vessel diameters were larger in lesions with a poor response to multiple sessions of SCS-SLP compared with lesions with a good response.[29,32] To circumvent this problem, it has been hypothesized that multiple cryogen spurts applied intermittently with

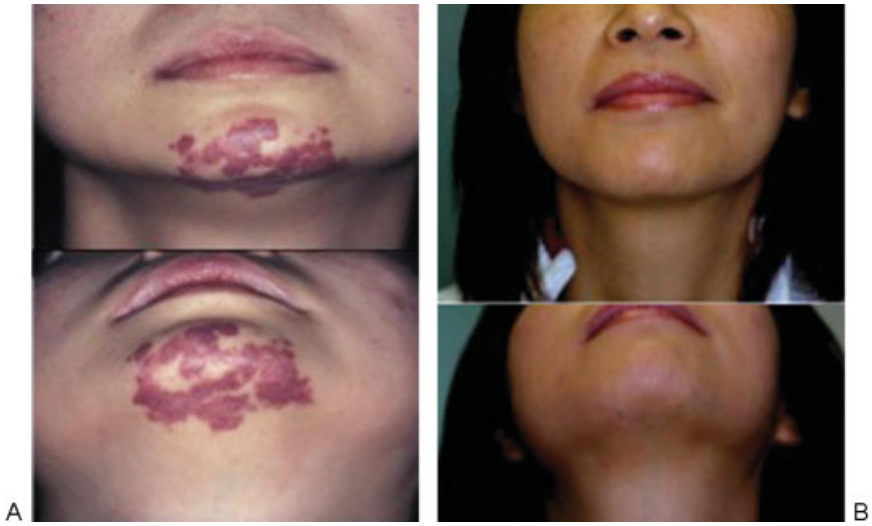

Figure 4 (A) A port-wine stain on the chin of a patient. (B) Great response after two treatments with a pulsed dye (585 nm) laser.

multiple laser pulse exposures (MCS-MLP) might not only be safer than SCS-SLP but could also improve PWS therapeutic outcome. When using SCS-SLP, all energy is delivered in a single laser exposure and thus the threshold for epidermal damage will always limit the maximum light dose that can be safely applied. In contrast, MCS-MLP distributes the laser energy into multiple pulses of lower energy, which avoids the inherent risk of overdosing and damaging the epidermis because the latter is actively cooled between successive MLP. Whereas the MCS maintain the epidermal temperature well below the damage threshold, delivery of MLP increases the core intravascular PWS blood vessel temperature because of significant heat accumulation in the vessels with each successive laser pulse. The pulse repetition rate is key in accumulating heat with each successive pulse in the targeted PWS vessels. In conclusion, the MCS-MLP approach is expected to be more effective than SCS-SLP because the total amount of light energy that can be delivered safely to PWSs is higher.

Preliminary animal studies have shown that larger vessel ($\sim$ 150-µm diameter) injury can be achieved using MLP (five pulses, 3 J/cm^2, 27 Hz) when single-pulse irradiation (4 J/cm^2) previously failed.[33] Although further investigation is required to determine the optimal parameters of MLP-MCS, such methodology is a promising new approach for treatment-resistant PWSs.

Multiple Pass Laser Treatment

Multiple pass laser irradiation for treatment-resistant PWSs is based on the concept that the first pulse (590 to 600 nm, 1.5 milliseconds) targets deeper and larger vessels whereas the second pass (585 nm, 0.45 milliseconds) targets more superficial and smaller vessels, increasing the efficacy of treatment of hypertrophic PWSs.[34] These results have not always been reproducible.[35] Moreover, the advantages of this technique have yet to be determined, and it is unclear whether the increase in efficacy is related to biochemical interactions between the two pulses.

By using multiple consecutive laser pulses separated by a time interval (i.e., 10 seconds), subthreshold radiant exposures are required for PWS clearing compared with a single laser pulse.[20] The authors have used multiple passes with different pulse durations to target blood vessels of varying sizes within the same treatment visit. Therapeutic outcome may be enhanced through more homogeneous dermal heating from heat propagation of dermal blood vessels with consecutive pulses.[36] Multiple laser passes optimizes treatment of deeper vessels and/or vessels that are optically shielded by adjacent surrounding vessels by favoring damage to PWS blood vessels from heat propagation of neighboring heated blood vessels.[36] Assuming treatment failure due to inadequate heating of shielded and deeper vessels, multiple pulses may be favorable compared with single pulse treatments.

Alexandrite Laser

Although PDL is the gold standard for treatment of PWS birthmarks, complete clearance is difficult to achieve. Over time, most PWSs will reach a treatment response plateau termed "treatment resistance."[37] One factor that contributes to treatment resistance is the limitation of PDL to treat PWS vessels located deep in the dermis. If PWS persist into adulthood, they may become hypertrophic and darken due to decreased sympathetic innervation that produces progressive vessel ectasia. These thicker lesions are also less responsive to PDL. Such lesions may respond to near-infrared lasers, such as a 755-nm alexandrite laser, which has selective absorption of deoxyhemoglobin over oxyhemoglobin and 50 to 75% deeper tissue penetration than PDL. The 755-nm laser may be used alone or in combination with PDL for improved efficacy of treatment-resistant PWSs or hypertrophic lesions (►**Figs. 5** and **6**). The combination of PDL and alexandrite laser treatment produces more rapid and increased lightening of hypertrophic PWSs without an increase in complications.[38] It is important to warn patients that permanent hair reduction may occur from treatment with the alexandrite laser.

Neodymium:Yttrium Aluminum Garnet Laser

Other near-infrared lasers, such as the 1,064-nm neodymium:yttrium aluminum garnet (Nd:YAG) laser, are not ideal for treating PWSs due to preferential damage to arteries rather than veins. However, the 1,064-nm laser has a higher

Figure 5 (A) A hypertrophic port-wine stain before treatment. (B) Tremendous improvement after six treatments with an alexandrite (755 nm) laser and concurrent pulsed dye laser. (Reprinted with permission from Izikson L, Nelson JS, Anderson RR. Treatment of hypertrophic and resistant port wine stains with a 755 nm laser: a case series of 20 patients. Lasers Surg Med 2009;41:427–432.)[38]

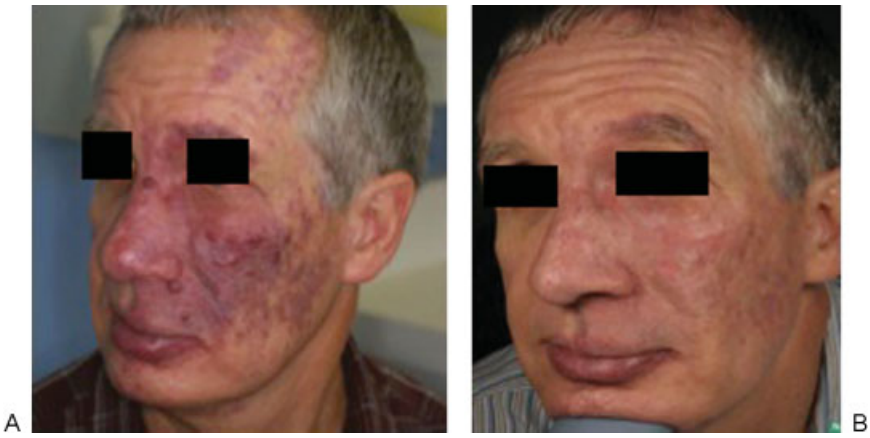

Figure 6 (A) A hypertrophic port-wine stain prior to therapy. (B) Vast improvement after six treatments with an alexandrite (755 nm) laser and concurrent pulsed dye laser. (Reprinted with permission from Izikson L, Nelson JS, Anderson RR. Treatment of hypertrophic and resistant port wine stains with a 755 nm laser: a case series of 20 patients. Lasers Surg Med 2009;41:427–432.)[38]

absorption coefficient of blood compared with the surrounding dermis, which provides treatment selectivity of deeper blood vessels ($\geq$ 2 mm), making it a better treatment option for hypertrophic PWSs than PDL.[37] Thermal injury of deeper blood vessels may lead to necrosis of the surrounding dermis and increases the risk of scarring compared with treatment with the PDL. This may be explained by the partial conversion of oxyhemoglobin to methemoglobin after photocoagulation by 1,064-nm Nd:YAG laser irradiation, which leads to increased absorption by laser fluences and a very steep fluence-response curve. Rapid changes in skin response may be avoided by using energies below the minimum purpuric dose.[37]

KTP Laser

Frequency-doubled Nd:YAG 532-nm lasers, known as potassium titanyl phosphate (KTP), emit green light near the hemoglobin absorption peak and may be used for PWS treatment. The 532-nm laser has more melanin absorption than PDL and may lead to scarring and dyspigmentation. However, frequency-doubled Nd:YAG lasers have been shown to be effective in PDL-resistant PWSs.[39] Dual-wavelength systems combining the Nd:YAG and KTP lasers have also been proposed to optimize treatment. The 532-nm wavelength induces heating and coagulation, and the 1,064-nm wavelength increases the temperature rise in the blood vessels compared with the 532-nm laser alone, which leads to bulk heating and methemoglobin formation. Theoretically, this should lower the risk profiles of both lasers when applied below their respective therapeutic thresholds. However, the responses have been similar to KTP treatment alone.[40]

Intense Pulsed Light

Intense pulsed light (IPL) systems use flashlamps and bandpass filters to emit noncoherent broadband light with wavelengths ranging in the visible to near-infrared range (400 to 1,200 nm). Theoretically, the advantage of using an IPL device over PDL is the ability of IPL to produce variable pulse durations along with multiple split light pulses. This causes heating of vessels of different diameters. Another advantage is the ability of IPL to emit multiple wavelengths that potentially target the full range of the hemoglobin absorption peaks, leading to destruction of both superficial and deep components of PWS.[41]

IPL has been shown to be safe and effective for the treatment of PWSs. A split-face comparison of IPL with dye lasers for the treatment of PWSs found significantly better improvement with IPL compared with the short-pulsed dye laser.[42] However, results were comparable between IPL and a long-pulsed dye laser. Another side-to-side comparison study of PDL and IPL for the treatment of PWSs showed that PDL still achieved better clearance rates than IPL.[43] Other studies have found improvement after IPL treatment of PDL-resistant PWSs although lesions in the V2 distribution of the face seem to be unresponsive to IPL.[44] Although IPL works reasonably well for PWSs, PDL remains the treatment of choice for the treatment of newborns and darker skin types where a dynamic cooling device (DCD) offers a higher level of epidermal protection. In PDL-resistant PWSs, lesions may benefit from IPL therapy.

Photodynamic Therapy

Photodynamic therapy (PDT) has been employed for the treatment of PWSs to attempt to improve the degree of PWS blanching following PDL therapy alone. During PDT, a photosensitizing agent is administered to the patient as an exogenous chromophore. After an optimal time interval, the tissue-localized drug is irradiated at an appropriate wavelength for selective absorption by the photosensitizer. This leads to a photochemical reaction, such as the generation of reaction oxygen species, which causes irreversible damage to the targeted tissue.

Early studies show that an exogenous photosensitizer in combination with light can cause selective destruction of vascular lesions in the dermis without damage to the normal overlying epidermis.[45] Compared with vascular photothermal destruction by lasers alone, which deliver short pulses (milliseconds) at high irradiance, destruction of PWS vessels

by PDT is accomplished without heat generation. PDT uses a laser or light source to drive the photodynamic reaction with milliwatt light exposure, avoiding epidermal injury and long exposure times (minutes) to ensure a sufficient dose in the targeted structure.[46]

Disadvantages of PDT for the treatment of PWSs include the need for a systemic photosensitizer leading to persistent generalized skin sensitization. Benzoporphyrin derivative monoacid (BPD) is a second-generation photosensitizer that has rapid metabolic clearance, which reduces the duration of skin photosensitivity and is vascular specific.[47–50] Animal model studies with BPD and yellow light have demonstrated selective vascular destruction including microvessels, which are spared by photothermolysis.[46,51] BPD has strong absorption at 576 and 690 nm that can be targeted by yellow and red light, respectively, for progressively deeper PDT treatments. Given that all vessels containing photosensitizer are destroyed with PDT, this potentially could lead to skin ulceration, necrosis, and permanent scarring from destruction of the lower vascular plexus. This may be avoided with the use of yellow light for the PDT light source that affects the upper 500 μm of the dermis.[52]

Combined Use of Laser and Agents to Modulate the Wound-Healing Response

Treatment resistance of PWSs is in part due to the regeneration and revascularization of PWS blood vessels following laser exposure. This may even result in darker, more noticeable lesions. The normal wound-healing response of human skin to laser-induced vascular photothermolysis is incompletely understood, prompting interest in modulating the neovascularization skin response to laser damage and increasing the duration of laser effects.

Rapamycin (RPM) is a specific inhibitor of mammalian target of rapamycin (mTOR) that is a natural macrolide antibiotic derived from *Streptomyces hygroscopicus*. RPM is currently approved by the Food and Drug Administration for use as an immunosuppressive agent to prevent allograft rejection in organ transplantation[53] and for coating coronary stents to prevent restenosis.[54] RPM is thought to have antiangiogenic properties through downregulation of hypoxia-inducible factor (HIF-1α), which acts as a transcriptional factor that regulates vascular endothelial growth factor (VEGF) expression.[55,56] Thus, RPM leads to a decrease in VEGF production and a reduction in the response of vascular endothelial cell to stimulation by VEGF.[57,58] Hypoxic microenvironments can cause overexpression of HIF-1α, which promotes platelet-derived growth factor[59] and VEGF.[60] Therefore, inhibition by RPM of the mTOR–HIF-1α–VEGF pathway is a promising intervention to prevent vascular reperfusion after laser irradiation.

RPM could potentially modulate the skin wound-healing response after light-induced photothermolysis by inhibiting the reformation of blood vessels. A phase I preliminary study on the test sites treated with the combined PDL and oral RPM (PDL + RPM) as compared with PDL alone has now been initiated and maintained long term for more than 13 months after treatment with no adverse effects.[61]

Given the promising results with systemic RPM, topical formulations are being developed to reduce the risks of systemic drug exposure. Animal studies show that when blood vessels in rodent skin were exposed to laser and topical RPM for 14 days, there was no reformation and reperfusion of blood vessels after light-induced photothermolysis (without topical RPM, reformation and reperfusion of the blood vessels were completed within 10 days post-laser irradiation).[62] Even after RPM treatment was discontinued for 14 days, no revascularization was observed in the animals during this period. Reperfusion rate does not seem to be linearly proportional to RPM concentration, for example, 1% RPM ointment seems to be more effective in inhibiting reperfusion than 2% or 0.5%.[63] This phenomenon is not yet fully understood.

Preliminary human studies on normal skin have also shown inhibition of regrowth of blood vessels in the skin after combined laser and topical RPM treatment.[64] Skin lymphatics were noted to be entirely collapsed in RPM-treated skin compared with the more ectatic lymphatics seen in skin treated with laser alone. This is suggestive of inhibition of both vascular leak and dermal edema with RPM. Therefore, RPM can modulate the wound-healing response and revascularization of human skin and extend the effects of laser exposure. The mechanism may be attributed in part to an inhibition of endothelial cell proliferation that leads to a decrease in the overall blood vessel density. RPM is effective at inhibiting revascularization of both the superficial and deep vascular plexuses and increasing efficacy of laser treatment that only partially photocoagulates the deeper vessels. This implies that lower light dosages may effectively treat lesions with combined topical RPM. Of note, topical RPM alone without laser irradiation does not affect the vasculature.[63]

Most recently, a study evaluating imiquimod 5% cream applied 3 times a week for 8 weeks immediately after PDL treatment of PWSs compared with PDL alone indicated a greater reduction in erythema and color improvement of PWSs.[65] Imiquimod exerts its antiangiogenic effect via activation of toll-like receptor 7, which induces antiangiogenic cytokines (interferon-α, interleukin [IL]-10, IL-12, IL-18) and reduces angiogenic stimulators (matrix metalloproteinase-9 and basic fibroblast growth factor). Treatment with imiquimod was well tolerated, except for only minor irritation.

Conclusion

Relationships between laser parameters and their effect on PWS treatment outcome are complex and continue to be incompletely understood. PWSs are commonly treatment-resistant to PDL, and new methodologies of treatment are urgently needed to optimize absorption of laser light by hemoglobin, heat transfer into the entire vessel wall, and coagulation of the blood vessel wall. The vast heterogeneity in terms of PWS blood vessel size and depth along with revascularization make it very difficult to eradicate lesions completely with current PDL technology. Increased understanding of interactions between PWSs and PDL has led to the development of new therapeutic modalities, such as the

combined use of antiangiogenic agents following laser irradiation. RPM has been shown to modulate the wound-healing response seen after laser irradiation by inhibiting revascularization and extending the effects of laser exposure. The new standard of care for PWSs may include a combined approach of laser therapy for initial vascular destruction and antiangiogenic agents to modulate biological repair processes. Larger prospective, comparative, and controlled clinical studies, however, are still needed to better define the role of antiangiogenic agents in conjunction with PDL therapy for the treatment of PWSs. Newer approaches will hopefully lead to better solutions for ineffective PWS treatment and lesion recurrence.

Editor's Comments: The range of conditions involving a cutaneous capillary malformation is large and the laser technology to deal with them is ever-evolving. This article, from one of the leading laser technology experts, expands on the most effective wavelengths for treatment of PWSs and future directions in combination with medical therapy.

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