Vascular Lasers and Lights

Introduction

Vascular lasers and lights have evolved considerably over the last thirty years since Anderson and Parrish published their landmark paper on selective photothermolysis.[1] Previously, continuous wave (argon and copper vapor) lasers were used to treat vascular lesions, but resulted in significant side effects such as scarring or pigmentary changes. With the understanding that laser energy can be modified for preferential absorption by the intended target, or chromophore, heat could be delivered in a more controlled manner that did not result in destruction of surrounding tissues. The laser wavelength could be matched to the absorption spectra of the targeted chromophore. By the 1990's, the pulsed dye laser (PDL) was established as the gold standard for vascular lesions.[2] Its wavelengths of 577-595 nanometers match the spectrum for oxyhemoglobin, which is in blood vessels. **Figure 1** demonstrates the absorption spectra of hemoglobin. The 532 nm wavelength has also been explored for its strong absorption by hemoglobin.

Using the pulsed dye laser, longer wavelengths can be used to target deeper structures. Likewise, longer pulse durations are used to sufficiently heat larger vessels. This is based on the principle of thermal relaxation time (TRT). The pulse duration (also called pulse width) should approximate the vessel thermal relaxation time, defined as the time required for the affected tissue to lose half the heat it gained from the laser. The thermal relaxation time of a vessel is proportional to the square of its diameter. Pulses which are too short will result in insufficient heating of the vessel, and pulses which are too long can result in excess heat diffusion which can adversely affect surrounding structures.

Childhood Hemangiomas and Port Wine Stains

The earliest application of these lasers has been in the treatment of childhood hemangiomas and port wine stains. Both conditions can result in serious psychological effects for the affected child and should be treated as soon as possible. Although hemangiomas of infancy can often involute, port wine stains continue to grow in thickness and usually darken in color. In this chapter we focus on the evidence supporting the use of different lasers (and parameters) to treat simple, refractory, and hypertrophic vascular anomalies. A discussion of the use of lasers in treating leg veins will also be included.

While the 1990's saw a shift from argon and copper based technologies to the pulsed dye laser, the first decade of the 21st century showed an exploration of second-generation pulsed dye lasers with slightly longer wavelengths, higher fluence, and longer pulse duration , in order to treat recalcitrant PWS and hemangiomas. The use of cryogen spray and contact cooling not only increases patient comfort but also protects the epidermis from thermal injury as the laser penetrates the skin. Other modalities such as intense pulsed light sources, long pulsed alexandrite and infrared lasers have been tried for refractory lesions. The use of lasers in darker skin types has also been investigated. Newer techniques have involved combining injectable photosensitizers with PDL to create photodynamic therapy (PDT) for vascular lesions. Topical agents like imiquimod and rapamycin have also been investigated. The following studies will summarize our present knowledge and practices for each of these modalities.

Consensus Documents and Guidelines

A limited Medline search was conducted using the following terms: (vascular) laser, port wine stain, hemangioma, and leg vein. Two recent sets of guidelines were identified. Most of these documents include protocols for diagnosis and imaging as well as treatment. For the sake of limiting this discussion to vascular lasers, we will focus on their recommendations for laser treatments specifically.

The European Society for Laser Dermatology published guidelines for care using vascular lasers and intense pulsed light (IPL) sources in 2007.[3] These guidelines were assembled by members of the dermatology departments in Sweden, Switzerland, Germany, and Slovenia. They begin by stressing the importance of properly diagnosing vascular lesions, emphasizing that arterial malformations should never be treated with laser or IPL. Careful attention should be paid to the lesion being treated, the skin type, and the anatomic location so that the correct parameters are chosen. Test treatments are advised. Their treatment principles include the following: 1) Smaller vessels need shorter pulses; larger vessels need longer pulses; 2) The deeper the blood vessel is located in the dermis, the larger the spot size, the longer the wavelength and the longer the pulse duration should be, combined with cooling to protect the epidermis; and 3) Darker skin types need longer pulses and longer pulse intervals.

The authors provide guidelines for treating a variety of congenital and acquired vascular lesions. Most benefit from treatments every 4-6 weeks and patients should avoid sun exposure prior to and after laser treatment. Areas prone to scarring, such as the anterior chest or neck, or where skin is fragile such as periorbitally should be treated with a 10-20% reduction in fluence. **Table 1** outlines their laser recommendations for a variety of different conditions, including conditions such as telangiectasias, rosacea, venous lakes, leg veins, port wine stains and hemangiomas of infancy.

For hemangiomas of infancy, which can have long-lasting psychosocial effects, they recommend treating all hemangiomas with laser as early as possible (**Figures 2a, 2b**). This helps prevent the proliferative phase and its associated complications such as ulceration, bleeding, or infection. The authors remind readers that laser treatment will only affect the superficial component of the hemangioma and that it is often difficult predicting whether there will be a deep component.

Port wine stains are vascular malformations which continue to increase in size throughout life. Unlike hemangiomas, they do not involute. Some remain as pale, erythematous macules or patches while others grow rapidly during adolescence. The authors recommend starting laser treatment as soon as the PWS turns darker or thicker. This is because smaller PWS (less than 20cm^2) clear better than larger ones, irrespective of age. However pink PWS, especially in children, are more difficult to lighten than mature red PWS. Thus clinical experience must be used to establish starting time. Deep purple and nodular PWS respond least well to laser treatment; longer wavelengths (755 nm, 800-900 nm, and 1064 nm) are more suitable. Other guidelines mention that PWS on the distal extremities are more difficult to clear than on proximal extremities, centrofacial lesions (and those in the V2 distribution) are less responsive to laser therapy than PWS located more laterally on the face, and PWS on the head and neck respond better to laser treatment than lesions elsewhere on the body (**Figure 3a and 3b**).

For treatment of leg veins, lasers are less successful on the legs due to increased hydrostatic pressure, thicker surrounding adventitial tissue, greater depth in the dermis, and more energy required to target vessels (with greater resultant damage to overlying epidermis). Because of the need for longer wavelength, the Nd:Yag (1064 nm) has emerged as the laser of choice for leg veins. The authors recommend that lasers be considered prior to sclerotherapy only in patients with needle phobia, who fail or don't tolerate sclerotherapy, or who are prone to telangiectatic matting. Fair skinned individuals whose feet and ankles have numerous vessels <2mm may also be treated with laser.

Table 1: Guidelines for care from the European Society for Laser Dermatology (2007)

Vascular Lesion	Recommended Laser	Notes
Facial telangiectasias	1st choice:FPDL, KTP (532), IPL 2nd choice: APDL, argon, copper vapor (with great care)	Contact cooling or topical anesthetic recommended
Rosacea	1st choice: FPDL, KTP (532), IPL 2nd choice: APDL, argon, copper vapor (with great care)	The erythema (first stage of rosacea) can only be treated with FPDL, KTP, or IPL.
Hemangiomas of infancy	1st choice: FPDL, IPL, Nd:Yag, KTP	Patients older than a year can be treated with topical anesthetic or nerve blocks.
Port Wine Stain (PWS)	1st choice: FPDL, IPLS, Nd:Yag, KTP (large spot)	
Spider Angiomas	1st choice: KTP, FPDL, IPLS, Nd:Yag 2nd choice: argon, copper vapour	Occurs in 15% of normal individuals. More common in children, pregnancy, liver dz
Poikiloderma of Civatte	1st choice: FPDL, IPL 2nd choice: KTP (caution to avoid scarring depending on area)	Reduce the fluence when treating scar-prone areas such as chest and neck, with larger spot sizes
Venous Lakes	1st choice: KTP, Nd:Yag, FPDL, IPL	Dilated venules without the proliferation of vascular tissue
Cherry Angioma	1st choice: KTP, Nd:Yag, IPL, FPDL	Disappear in extreme old age
Leg Veins and telangiectasias	1st choice: Nd:Yag (1064) 2nd choice: For small diameter (<1mm) can use KTP, FPDL (long pulse),IPL 2nd choice: For large diameter can also use Nd:Yag, alexandrite, diode, IPL	Overall, lasers are second choice after sclerotherapy

Another set of guidelines was published in 2008 by the German Society of Dermatology together with the German Societies for Pediatric Surgery and Pediatric Medicine.[4] This focused specifically on the treatment for hemangiomas of infancy and childhood, and included recommendations for non-laser therapies as well. They based their recommendations for treatment on the phase of hemangioma growth. Rapidly proliferating hemangiomas, and especially those located in problematic areas such as near the eye or anogenital region, should be treated promptly. Likewise, lesions which may ulcerate should be treated promptly (**Figures 4a, 4b**). However, hemangiomas in the quiescent or regression phase may take a ‘wait and see’ approach.

The authors describe laser therapy as the best approach for flat hemangiomas. Specifically, flashlamp-pumped pulse dye laser (FPDL) or intense pulsed light (IPL) with resultant purpura can help resolve the lesions. Scars are reported to occur in 1% of cases. No specific recommendations for laser settings or treatment intervals are provided. They discuss the Nd:Yag as helpful for greater penetration of subcutaneous hemangiomas. It can be used with topical cooling or intralesionally via quartz fibers. Such treatment may help reduce the volume of very large hemangiomas before a planned surgical procedure. The authors also discuss cryotherapy for flat lesions, stating that the results are comparable to those of laser therapy. Systemic corticosteroids or cytotoxic agents can be used in cases of very rapidly proliferating (**Figures 5a-5c**) or life-threatening hemangiomas.

Less recent guidelines are available from the American Academy of Dermatology, which were written in 1997.[5] They recommend the use of flash-lamp pumped pulsed dye lasers but urge caution in lasers such as the argon which may result in hypopigmentation or scarring. These guidelines will presumably be updated soon to reflect the enormous advances in laser technology since they were written.

Case Series and Cohort Studies

Several large studies dating back 10 years have established the role of the flashlamp-pumped dye laser in treating port wine stains and hemangiomas. A case series of 617 cases of mostly superficial childhood hemangiomas using the 585 nm PDL with .45ms pulse duration reported the cessation of further growth in 96.6% of patients.[6] However, side effects included blister formation, crusts, and pigment changes in 7% of patients as well as 4% with small atrophic scars, likely due to the fact that contact cooling had not yet been introduced. Another study showed that the deeper component of mixed hemangiomas responded less well to the 585 nm, due to the limited penetration of the PDL (.8-1.0mm).[7] The subcutaneous components were recalcitrant to treatment and even continued to proliferate in most cases. The benefits had to be weighed with the side effects of pigmentary and textural changes.

Darker skin types also faced a dilemma in that their epidermal pigmentation provided a barrier to laser penetration. They risked blister formation or scarring where the laser energy was absorbed. In one 2002 study of 107 Chinese patients who were randomized to treatment with the 585 nm PDL, the 532 nm KTP, or both, the authors found that they were less responsive to laser treatment, required more treatments, and had a higher complication rate.[8]

Another interesting problem with the lasers was that these deeper, incompletely treated lesions could re-emerge years later. Redarkening of port wine stains 10 years after pulsed-dye-laser treatment was reported in 18 of 51 patients (35%).[9] They were still lighter than they had been prior to treatment, but darker than after the treatments were finished. Another larger study found that 15 of 110 (13.4%) patients treated with 585 nm laser for port wine stains found their lesions to re-emerge.[10] These areas re-emerged an average of 31.3 months after discontinuing treatment. Spider nevi can also recur, and one 2-year study found that 50 out of 139 patients (36%) questioned 27-51 months after finishing treatment reported a recurrence.[11] The most common time for return was between 6 and 18 months.

The challenge, therefore, was to find ways to reduce side effects, increase penetrance, and reduce recurrence of these lesions. These techniques included the introduction of contact cooling, which allowed for higher fluences to be used. Increasing the wavelength allowed for the delivery of energy to the deeper vessels, and increasing the pulse duration allowed for the treatment of larger vessels.

Contact Cooling

In 2000, Geronemus used a modified pulsed dye laser with a tetrafluoroethane spray prior to and just after each laser pulse, to treat sixteen infants with facial port wine stains.[12] In this same group, he increased the pulse duration to 1.5ms and increased the energy fluence to 11-12 J/cm^2. Sixty-three percent had a greater than 75% clearing after an average of 4 treatments. Although it was only a pilot study, the multiple modifications made set the stage for investigating many different paramaters.[12]

Asian patients were found to benefit from the use of cryogen spray cooling in that their darker skin was protected from the effects of the laser. One prospective, split-area study from 2003 compared the use of the 585 nm PDL alone versus the 585 nm laser with cryogen spray cooling to treat port wine stains in 35 Chinese patients.[13] It found that patients treated with cryogen spray achieved greater clearance, probably because significantly higher fluences could be used. Pain scores were higher and blistering more common in the PDL alone-treated group. Overall, patients preferred the cryogen spray for its increase comfort and greater clearance.

By 2007, a retrospective report described 49 facial port wine stains in newborns which had all improved with the 595 nm wavelength, at 1.5ms and at fluences of 7.75-9.5J/cm^2 and the use of cryogen cooling.[14] The clearance for the V1 distribution was highest (93.8%), followed by V2 (91.1%) and V3 (84.3%). No cases of atrophy or scarring resulted and the authors remarked that this was an excellent option for patients 6 months of age or younger (**Figures 6a, 6b**). Since then, a 2009 retrospective chart review of 90 patients with 105 hemangiomas reported excellent clearing with the 595 nm long-pulsed dye laser with dynamic epidermal cooling at 2-8 week intervals.[15] Near-complete or complete clearance in color was achieved for 85 (81%) of lesions and in thickness for 67(64%) of hemangiomas. No instances of scarring or atrophy occurred, but hyper- and hypopigmentation occurred in 4% and 14% of hemangiomas respectively.

Changing Wavelength

In 2001, a study of 62 patients with untreated port wine stains compared the traditional 585 nm, 45ms pulsed dye laser with a longer-tunable dye laser (585-600 nm) which demonstrated just as optimal fading and no side effects so long as the epidermis was additionally cooled with a spray cooling device.[16]

The use of the 595 nm wavelengths in darker skin types has also proven to be helpful. A 2006 case series of 239 Korean patients (Fitzpatrick skin types III to V) were treated with the 595 nm PDL, 1.5ms pulse duration for nevus flammeus, telangiectasias, or hemangiomas.[17] Over half (51.9%) of patients had either good (51-75%) or excellent (76-100%) clearance. As with the Caucasian populations, lesions on the head and neck responded more favorably, and superficial hemangiomas showed a better clinical response than deep hemangiomas. Hyper- and hypopigmentation was noted in 10 (27.2%) and 2 (5.4%) of patients. Another study published the same year showed that of 66 Japanese patients treated with the 595 nm for PWS, 67% had a good or excellent response.[18]

Prior to this, the potassium titanyl phosphate (KTP) 532 nm laser was used to treat vascular lesions. A Polish case series published in 2005 found that 81% of 155 patients had fair (23%), good (27%), or excellent (31%) improvement.[19] There were no reports of scarring or persistent pigmentary changes in the epidermis. The laser worked best on lesions localized to the face and neck; lesions on the trunk and extremities were quite resistant. A prospective cohort of 30 patients in the UK treated for PDL-resistant port wine stains found that 16 patients (53%) had a >25% response and 5 patients (17%) had a >50% response.[20] Patients preferred the KTP citing less discomfort and minimal purpura. Six patients had side effects, including scarring in 2 (7%), hyperpigmentation in 3(10%) and prolonged healing phase over 4 weeks in 1 (3%).

The frequency doubled neodymium:yttrium-aluminum-garnet (Nd:YAG) 532 nm laser was also investigated for treatment of vascular lesions. A Turkish case series of 89 patients treated for port wine stains found that results were excellent (>95% improvement) for 13% of patients, good (75-94% improvement) in 38% of patients, moderate (50-74% improvement) in 44% of patients, and mild (25-50% improvement) in 5%.[21] Side effects included hyperpigmentation in 2 patients (2.25%), hypopigmentation in 1 patient (1.12%) and atrophic scarring in one patient (1.12%). When the frequency doubled Nd:YAG (532 nm) laser was compared with the 585 nm laser in a retrospective trial of 50 infants with 62 superficial hemangiomas, a cessation of growth was achieved in 93% and 70% of the PDL and Nd:YAG treated lesions, respectively.[22] Complete regression was seen in 41% of the PDL treated lesions and 30% of Nd:YAG treated lesions. Because the PDL was more effective, the authors concluded that PDL was still the preferred therapy for hemangiomas.

The frequency-doubled Nd:YAG 532 nm laser was tried in the treatment of port wine stains in Chinese patients, but a retrospective review of the 22 treated patients demonstrated just 33% of patients with more than 50% clearing and 62% of patients with more than 25% clearing.[23] Pigmentary and texture changes were noted in 11-33% of patients, and very high fluences were required to achieve clearing. The authors concluded that Nd:YAG was only partially effective for the treatment of PWS in Chinese patients and that while contact cooling help protect the epidermis, textural changes could still occur.

Increased Fluence

A prospective case series reported using a high-energy device that delivered 9.5J/cm^2 at 595 nm with a 1.5ms pulse duration and 10mm circular spot.[24] Twenty patients with port wine stains that had become refractory to the conventional 585 nm laser were included in the study and had an average improvement of 76% following an average of 3.1 treatments.

The tradeoff with increased fluence is the appearance of greater purpura postoperatively. This appearance of bruising can limit patient acceptance but has been shown to increase clearing. A prospective, randomized controlled trial of 11 patients with facial telangiectasias demonstrated a greater improvement in areas treated .5J/cm^2 above the purpura threshold than patients treated 1J/cm^2 less than the threshold.[25]

Another suggestion has been the use of pulse stacking (repetitive treatments at a lower fluence) to improve results without causing the same degree of purpura. In a randomized study, 25 patients underwent a single 595 nm pulse on one cheek and 3-4 pulses on the opposite cheek.[26] Both sides used the sub-purpuric fluence of 7.5J/cm^2 and greater clearance was noticed on the pulse-stacked side. This remains an option for patients who do not want to have postoperative purpura. One case of edema was noted in the pulse-stacked group.

Increased Pulse duration

In 2005, a longer pulse duration of 1.5ms was also found to increase the efficacy of the 585 nm laser for treating port wine stains, in a study of 95 patients with 104 areas of involvement by PWS. Twenty-one of these patients had failed previous treatment using a conventional .45ms device, but showed improvement with the longer pulse duration.[27] A comparative study of 18 patients, examining the use of the 595 nm laser with the 585 nm lasers at the same pulse duration of 1.5ms demonstrated little difference between the two settings, but found that the use of even longer pulse durations (6ms) yielded no significant advantage.[28]

Another prospective study compared the use of two wavelengths (585 nm and 595 nm) as well as two pulse durations (.5ms and 20ms) in 15 patients with port wine stains.[29] They found that increasing the pulse duration all the way to 20ms with the 595 nm laser (and increasing the fluence to 13J/cm^2) conferred no additional advantage over simply using the 585 nm wavelength with the .5ms pulse duration at 5.5J. A uniform spot size of 7mm was used for all treatment groups. Overall, they found that purple PWS responded better than lesions which were red or pink.

Noncoherent Light Sources

Several studies have investigated the use of intense pulsed light (IPL) systems, which included a broad range of noncoherent wavelengths, to treat vascular lesions. The largest of these tested a 515-1200 nm IPL for rosacea in 60 patients, treating a total of 508 sites with an average of 4.1 treatments per site.[30] The patients had a mean clearance rate of 77.8% and over three years, recurrence was noted in only 4 or 508 treated sites. Four other, smaller studies examined the use of IPL for port wine stains. Their results are summarized in Table 2.[31-34]

Table 2: Summary of studies Using Intense Pulsed Laser for Port Wine Stains

Study	No. of patients	Study design	Outcome
Ozdemir et al, 2008[31]	12 Turkish patients with untreated facial and/or neck PWS	Patients received 3-6 treatments every 4-6 weeks	-Moderate improvement (50-75% clearing) was seen in 47% of patients -Complete clearing in only 1 patient (8.3%)
Reynolds et al, 2005[32]	12 British patients with untreated PWS on the body (less visible areas)	Treated with IPL cutoff filters of 550-1100 nm for 2-9 treatments, case-controlled within-patient	-8/12 had some degree of fading -4/12 had no response (and all had pink PWS) -Darker, more caudal lesions had a better response
Ho et al, 2004[33]	22 Chinese patients with untreated PWS	Treated 5-7 times at 3-4 week intervals	-9% achieve complete clearing -Majority (50%) had only 25-50% clearing
Bjerring et al, 2003[34]	15 Danish patients with PDL resistant PWS	Treated four times with 2nd generation IPL system and evaluated 2 months after last treatment	-46.7% of patients responded to IPL (had more than 50% clearance; 87% of these had 75-100% clearance) -53.3% did not respond to IPL (had less than 25% clearance) -V2 area did not respond to treatments

As indicated in Table 2, the IPL technology does not provide more than a moderate improvement in either previously treated or untreated port wine stains. Direct randomized controlled trials of PDL with IPL are described in the next section of randomized controlled trials, and indicate that PDL is still the best technology for treating vascular lesions.

Infrared Light Sources

One 2009 case series of 20 patients describes the use of the 755 nm alexandrite laser for treatment of hypertrophic and resistant port wine stains. They found that these lesions showed significant lightening after treatment with a 755 nm laser in combination with PDL, but not all were successful. Side effects included pain, edema, bullae, crusting, and rare scarring. Although the results were promising the authors urged their colleagues to be cautious choosing a fluence at or near the threshold for clinical response. The deeply penetrating nature of this laser could result in serious sequelae.[35]

One pilot open-label clinical study of 17 patients with port wine stains compared using 3 sessions each with the 595 nm PDL (1.5ms and dynamic cooling) and with the 1064 nm Nd:YAG laser.[36] Fluences 1.0, .8, and .6 times the minimum purpura dose were applied for the Nd:YAG group and both groups had similar clearing, but the Nd:YAG caused greater perivascular and epidermal injury. Again, the authors warn that Nd:Yag can be as effective but can cause scarring at higher fluences.

Perhaps the most interesting of recent studies has combined the use of the 595 nm PDL with the 1064 nm laser for treatment of recalcitrant and hypertrophic port wine stains in adults and children. Twenty-five patients who had incomplete clearance despite 10 previous treatments with PDL were treated by Alster and Tanzi using a novel device that delivers sequential pulses of 595 and 1064 nm wavelengths.[37] Additional clinical improvement was noted in all patients, although none had complete clearance. It was found to be slightly more uncomfortable by adult patients, but none had pigmentary alterations or scarring .

In describing their 20 years of experience in treating the pediatric population, Burns and Navarro describe how they use the 1064 nm Nd:Yag laser only on patients whose hemangiomas have begun to involute.[38] Otherwise, they noticed higher rates of skin ulceration and necrosis. They theorize that the proliferative lesions are already at higher risk for ulceration, and the laser heating can place an increased metabolic demand that hastens or even causes ulceration. Similar results are suggested by a 2006 publication reporting 12 patients who had complications following PDL for hemangiomas of infancy.[39] Eight developed ulcerations and four had permanent atrophic scarring. All were treated between the ages of 5 days and 4 months, when the hemangiomas were likely to have still been in the proliferative phase. However, 11 of the 12 were treated without any dynamic cooling to the surface, which may have resulted in more epidermal injury.

A direct comparison of the 755 nm alexandrite, 1064 nm Nd:YAG, 550-1100 nm IPL, and 532 nm KTP lasers with the PDL as control was performed in 18 patients with capillary malformations.[40] All 18 had received at least five treatments with a PDL 585 nm, for .45 ms to lesions on their head or neck, and received test treatments of all five different systems. The alexandrite laser showed the most improvement using Munsell color charts, improving 10 patients, while the KTP and Nd:YAG lasers were least effective, with fading seen in just two patients. Six patients improved with the IPL. Five had further fading with the PDL. The tradeoff was a higher rate of side effects seen in the alexandrite laser. Hyperpigmentation and scarring developed in four patients, likely due to the deeper penetration and lower specificity for oxyhemoglobin-carrying vessels.

Photodynamic Therapy

One relatively new area of study is the use of an intravenous photosensitizer prior to treatment with a laser. In 2007, 1949 cases of port wine stains in 1385 patients received IV hematophorphyrin derivative or hematoporphyrin monomethyl ethere (HMME) prior to undergoing laser irradiation with different wavelengths (488-578 nm) at varying fluences.[41] Among the treated lesions, 6.6% achieved 100% clearance, 38.3% achieved >75% clearance, and 47.4% achieved 50-75% clearance. Darker stains required two sessions or more, while pink PWS had better response with only one session. The authors reported almost no risk of scarring.

In 2009, 75 patients in China with port wine stains were injected with photosensitizer (Photocarcinorin, PsD-007) and exposed to copper vapor laser.[42] Complete clinical remission was observed in 57.3% of patients and some improvement was seen in 94% of patients after no more than four courses of treatment. Twenty percent of the complete responders required only two courses or less.

Adjunctive topical treatments

Imiquimod is a topical immune-response modifier which has been FDA approved for treatment of genital warts, actinic keratoses, and basal cell carcinoma. Its use in a variety of other skin conditions has been explored and in 2008 a pilot study examined its use in treating port wine stain birthmarks, alone and in conjunction with 585 nm PDL (1.5ms) for a group of 20 Asian patients.[43] In each patient, three test areas were identified for treatment: PDL alone, imiquimod alone, and PDL+imiquimod. PDL test sites received a single laser treatment of spot size 7mm using 10J/cm2 and cryogen spray cooling. For the imiquimod sites, the patients applied the agent once daily for 1 month after PDL exposure. They were followed at 1, 3, 6, and 12 months after the initial laser exposure, and a blanching response was evaluated using a dermospectrophotometer. They found that over time, the group treated with PDL and imiquimod had the best response ($P<.05$) with superior blanching over the other two treatment groups. No hypopigmentation or scarring was seen, and any hyperpigmentation resolved within 6 months.

Rapamycin is an anti-angiogenic agent which has been shown to inhibit growth of blood vessels. It was investigated in conjunction with laser pulses in golden Syrian hamsters to see whether it could inhibit reperfusion of photocoagulated blood vessels in an animal model.[44] Two treatment groups were established: one treated with laser only, and one treated with laser and then topical rapamycin daily for 14 days after laser exposure. In the laser only group, they found that 23 of the 24 photocoagulated blood vessels reperfused within 5-14 days. The combination treated group had 36% less reperfusion than the laser-only group. There was no correlation with the concentration of rapamycin used and the reperfusion rate, but the results suggest that topical anti-angiogenic therapy may help improve results with laser therapy.

Conclusions

-Pulsed dye laser remains the gold standard for treating vascular lesions. Side effects include purpura (transient) and ulceration in highly proliferative lesions.

-The 1064 Nd:YAG can also be used for PWS but should be used with caution due to the possibility of scarring at high fluences.[36] The combination of 595+1064 is especially promising.[37]

-The 532 nm wavelength can provide adjunctive therapy but has risk of pigmentary changes and scarring,[20-23,] especially in darker skin types.[23]

-Epidermal cooling is essential to help mitigate textural and pigmentation changes [14,15]

-Intense pulsed light (IPL) laser therapy can help lighten vascular lesions but is not a panacea.[31-34] The deeper components (>1mm) of HOI remain difficult to treat.

-Increasing the wavelength to 1.5ms with either the 585 or 595 PDL can improve results for refractory lesions.[27]

-Increasing the energy to 9.5J/cm^2 with the 595 PDL can improve results for refractory port wine stains.[24]

-The 595 nm PDL with 1.5ms pulse duration is presently the standard of care for PWS and HOI.

-Longer wavelengths (>6ms) confer no additional advantage in clearing the lesions.[28,29]

-Pulse stacking can provide comparable clearing without the purpura that results from using higher fluences.[26]

-Photodynamic therapy using photosensitizers prior to laser treatment can improve PWS.[41,42,50]

-Patients born with PWS should undergo treatment as early as possible and as many times are necessary to avoid hypertrophy and nodularity, which are more difficult to treat.

Randomized Controlled Trials and Meta-Analyses

A search of the Pubmed English literature for the terms "port wine stain," "hemangioma," and "telangiectasias" was conducted to identify all existing randomized controlled trials and meta-analyses for the last 10 years. The following includes a description of the findings. Many randomized controlled trials were identified, but there were no meta-analyses. As with most of the previous studies, these involved improving upon existing treatments for port wine stains and hemangiomas, including those which are hypertrophic or resistant to therapy.

In 2002, a randomized controlled study of early pulsed dye laser treatment for 121 infants with uncomplicated hemangiomas demonstrated no significant difference in the rate of clearing between treated and untreated groups.[45] The side effects of skin atrophy (seen in 28% of treated patients) and hypopigmentation (45% of treated patients) made the treatment not worthwhile. This study used traditional 585 PDL wavelength with a .45 microsecond pulse duration but with no epidermal cooling. We know from subsequent studies that the epidermal cooling is crucial to minimizing side effects.

By 2005, a randomized, blinded controlled study demonstrated a higher proportion of clearance when the pulse duration was near to or higher than the thermal relaxation time.[46] This was achieved by varying different pulse durations in patients treated with the KTP 532 nm laser for telangiectatic facial vessels. A 2006 prospective, randomized controlled trial enrolling 52 Japanese infants compared the clearance of hemangiomas treated with traditional pulsed dye laser (585 nm, with pulse duration=.45 milliseconds) with long-pulsed (595 nm, pulse duration 10-20 milliseconds) using cryogen spray cooling to protect the epidermis.[47] It found that the PDL group had 54% had complete clearance while the LPDL group had 65% clearance. Although this result was not statistically significant, the degree of side effects (hyperpigmentation, hypopigmentation, and textural changes) was significantly lower in the long pulsed PDL group. Likewise, the LPDL group had a significantly shorter time period of proliferation by the hemangiomas (177 days for PDL versus 106 days for LPDL).

Port wine stains can be quite refractory to laser treatment, even with longer wavelengths and increased pulse durations. The use of higher fluences, along with cooling of the epidermis was investigated in one randomized controlled trial in 2007. This study treated 11 patients with port wine stains which were partitioned into three areas.[48] All three areas were treated with 585 nm PDL, 1) 6J/cm^2 with no cold air cooling, 2) 6J/cm^2 with cold air cooling, and 3) 9J/cm^2 with cold air cooling. The third treatment group demonstrated a slightly but not significantly higher rate of clearance (59% versus 57%) than the first group. Because pain was also lowered, the authors recommended in favor of using contact cooling.

Another suggestion for improving results was to increase the frequency of treatments. In 2006, a British group enrolled 15 patients with port wine stains to compare treatments at 2- and 6-week intervals.[49] On their first visit the entire lesion was treated with a 595 PDL. Then, half the lesion was randomly allocated to be treated again after 2 weeks and the other half to be treated at 6 weeks. Both areas were examined by independent observers after 12 weeks and the endpoint was the degree of lightening as measured with a reflectance spectrophotometer. In 11 of the 13 patients who completed the trial, the two week treatment interval resulted in a significantly greater reduction in reflectance than the 6-week interval (P=.003) No adverse reactions were reported and the results suggest that shorter treatment intervals are more effective.

A randomized internally controlled trial of 8 patients with port wine stains combined the use of a photosensitizer (5-aminolevulinic acid) with a 585 nm pulsed dye laser to see if patients would achieve better clearance than in areas treated with PDL alone.[50] Five -ALA is a porphyrin deriverative which is converted in vascular endothelial cells to the active photosensitizer PpIX. One of the peaks in its absorption spectrum is 576 nm which has been utilized for the treatment of actinic keratoses. The researchers found no significant benefit from combining PDT with PDL. However, the authors suggest that further research in using longer pulse durations, higher fluences, or larger doses of 5-ALA may demonstrate better results.

Three randomized controlled trials investigated whether intense pulsed light sources could offer better treatment of vascular lesions than pulsed dye lasers. In the first study, twenty patients in Denmark with port wine stains were allocated to receive side by side treatments of 595 nm PDL treatment and IPL.[51] Treatment outcomes were evaluated by blinded observers and skin reflectance measurements. They found that the PDL treated group has significantly better clearance rates (75% vs. 30%) as well as better lightening on skin reflectance (33% versus 12%) than the IPL treated spots. Eighteen of the 20 patients preferred to continue treatments with PDL rather than IPL. No adverse events were reported in either group.

In a second study containing 20 patients, individuals with photodamaged skin were randomly assigned to receive LPDL (595 nm, with dynamic cooling and a 3-20ms pulse duration depending on the size of the vessels being treated) to one half-face and IPL (without cooling) on the other half of their face.[52] The patients received a series of three treatments at 3 week intervals, and were evaluated at end point for telangiectasias, pain, and adverse effects. Superior vessel clearance was observed via blinded clinical evaluations as well as patient self-assessments for the LPDL treated sides. Likewise, patients preferred the LPDL treatments over the IPL because it was less painful. Results of a third smaller but nearly identical split-lesion study comparing LPDL with IPL for telangiectasia after radiotherapy for breast cancer showed a significant improvement in vessel clearance with LPDL (90%) over IPL (50%).[53] Lower pain score and higher patient satisfaction were reported in among 11 of the 13 patients who enrolled in the trial.

One randomized controlled trial from 2009 compared non-purpuragenic PDL settings (595 nm, 6ms pulse duration) with IPL settings using 560 nm cutoff filter and chilled crystal tip to treat erythemotelangiectatic rosacea.[54] The fluence of the PDL was adjusted up or down to achieve transient purpura. Three monthly treatment sessions were performed in this single-blind split face trial of 29 patients. Both systems resulted in significant reduction of erythema, telangiectasia, and patient reported symptoms, with no difference noted between the two treatments.

Other modifications for improving response over the PDL included changing the wavelength to 532 nm with the potassium-titanyl-phosphate (KTP) laser (**Figure 7a, 7b**). Fifteen patients with facial telangiectasias were treated in a split-face, single-blind, controlled comparison study using the 595 nm PDL on one cheek and the 532 nm KTP laser on the opposite cheek.[55] They underwent three treatments, every three weeks, and were evaluated three weeks after the last treatment. The KTP laser achieved 62% clearing after the first treatment and 85% clearing at final evaluation, while the PDL achieved just 49% and 75% clearing for the same time intervals. However, the areas treated with the 532 nm laser noted 58% erythema while PDL treated areas had only 8%. This study suggests that the KTP laser is more effective for facial telangiectasias but causes more swelling and erythema.

Another randomized controlled trial published in 2010 investigated the use of PDL (595 nm), KTP (532 nm) and electrodessication for treating cherry angiomata.[56] Fifteen volunteers had three areas on the trunk demarcated with four lesions each. Each area was randomly assigned to undergo one of the three treatments, two times and spaced two weeks apart. The areas were analyzed for color and texture on visual analog scales. Lesions treated with electrodessication were significantly less improved than those treated with PDL (P=.001) and KTP (P=.003). No difference in textural change was noted between the KTP and PDL lasers. However, there was more textural change associated with electrodessication than with laser.

In 2008, researchers tested the combination of PDL (595 nm) and Nd:YAG (1064 nm) with PDL or Nd:YAG alone using a dual wavelength laser system for treatment of facial telangiectasias.[57] Twenty patients underwent the sequential delivery of PDL and Nd:YAG on one cheek, and were randomized to receive either PDL or Nd:YAG on the opposite cheek. Results were evaluated four weeks later by blinded assessment of before and after photographs. They found no statistical difference in efficacy between the single wavelength treated sides, but there was a significant improvement (P<.05) seen in the dual-wavelength group.

Conclusions

-The pulsed dye laser is still the best treatment option over the IPL for PWS and hemangiomas.

-Combined wavelengths of 595 with 1064 may allow improved penetration of deeper vessels (ref 12, ref 4b)

-The 532 nm KTP laser may be helpful in treating very superficial facial telangiectasias.

Lasers and Lights for the Leg Telangiectasias

The treatment of leg veins with vascular lasers is slightly more challenging. This has been attributed to several factors: 1) Lower content of oxygenated blood returning from the lower extremities to the heart

2) thick surrounding interstitial tissue and fibrosis surrounding the vessel walls, and 3) increased hydrostatic pressure in the lower extremities.[3] As a result, the most promising lasers have been in the near-infrared range, targeting 750-1100 nm.

Initial studies investigated the use of the 532 nm wavelength for treatment of leg veins. One randomized, controlled trial used the KTP lasers for spider leg veins in 70 female volunteers.[58] Three treatment sessions were provided each for vessels less than or equal to .6mm in diameter, and for vessels .7-1.0mm in diameter. They found that the smaller size vessels showed complete resolution in 33%, a decrease in vessel diameter in 40%, and no change in appearance for 27%. The larger size vessels were all still visible after 3 sessions. Hyperpigmentation occurred in 13 of the 56 patients who completed the study. Another study investigated the long-pulsed Nd:YAG laser at 532 nm with a chilled sapphire tip and found that it could treat leg veins of .5-1.0 mm diameter with greater than 50% clearance at 44% of sites with a single treatment.[59] Higher fluences of 16J/cm^2 improved the clearance rate but also had greater adverse effects, including atrophic scarring for up to a year.

The alexandrite (755 nm) laser has also been tried for leg veins. One 2002 trial involved treating twenty female volunteers (skin types 1-3) with .3-1.3mm leg telangiectasias with test spots of increasing fluence (40-90J/cm^2) and a spray cooling system.[60] They found that 15 out of 20 subjects had a clearance rate between 26 and 75%. Hyperpigmentation was observed in 15 patients, and hypopigmentation occurred in 2 patients. No edema, purpura, scarring, or blistering was seen. Another alexandrite study from 2009 enrolled 15 patients with .2-1.0 mm vessels (and skin types I-III) with varying pulse durations of 3 to 100 milliseconds.[61] Optimal settings were identified though blinded evaluation of pre and post treatment photographs. The average fluence required for vessel closure was 89J/cm^2 and the optimal pulse duration was 60 milliseconds for most patients. These parameters provided a clearance approaching 65% 12 weeks after a single treatment. Four patients did experience transient hyperpigmentation, but the study concluded that a longer pulse width reduced purpura and improved the side effect profile.

Investigation of the Nd:YAG 1064 nm laser has provided the most promising results for the treatment of leg telangiectasias. A 2002 side-by-side comparative study of the 1064 nm Nd:YAG, 810 nm diode, and 755 nm alexandrite lasers was performed in 30 female volunteers, skin types I-V, for .3-3mm leg veins.[62] In the 22 patients who completed the study, 36 sites were treated with the Nd:YAG laser, 18 sites were treated with the diode laser, and 12 vein sites were treated with the alexandrite. Greater than 75% improvement was seen in 88% of the Nd:YAG treated sites, 29% of the diode treated sites, and 33% of the alexandrite treated sites. Greater than 50% improvement was seen in 94% of Nd:YAG treated sites, 33% of diode treated sites, and 58% of alexandrite treated sites. Less than 25% improvement was seen in 6% of the Nd: YAG treated sites, 39% of the diode treated sites, and 33% of the alexandrite treated sites. Post-treatment purpura and telangiectatic matting was seen with the alexandrite laser. Overall the authors concluded that the Nd:YAG provided the best treatment with least side effects.

Optimal pulse durations for the Nd:YAG laser have since been identified as 40-60 milliseconds. A 2006 study of 18 patients with leg veins found that this provided clearance of 71% of vessels with a single laser treatment, and minimal post-inflammatory pigmentation.[63] Shorter pulse durations (<20ms) increased tendency for purpura and post-inflammatory pigmentation. One comparative study suggested that the Nd:YAG 1064 long pulse laser could yield results similar to policodanol .5% sclerotherapy in the treatment of small leg veins.[64] It involved treating 4 sites on each of 14 patients with .4-2mm veins: sclerotherapy alone, laser alone, sclerotherapy then laser, and laser then sclerotherapy. The best clinical results were seen with sclerotherapy followed by laser, but this improvement was not statistically significant over either modality alone.

Nonetheless, most dermatologists still use injectable sclerotherapy as their gold standard for leg vein treatment. A 2002 study comparing the long-pulsed Nd:YAG with sodium tetradecyl sulfate (STS) sclerotherapy in 20 patients with size-matched superficial leg telangiectasias found that the veins responded best to sclerotherapy, in fewer treatment sessions, than to long-pulsed 1064 laser therapy.[65] Other sclerosing agents include glycerin, which has been showed to provide a better, more rapid clearance of previously treated telangiectasias,[66] and liquid polidocanol which offers comparable results as STS,[67] but is not yet approved for use in the United States. Hypertonic saline is used by many doctors in the U.S. and has been found comparable to polidocanol in efficacy and patient satisfaction.[68]

Conclusions

-Sclerotherapy continues to be the gold standard for treatment of leg veins.

-The best laser for treatment of leg veins appears to be the long-pulsed Nd:YAG (1064 nm).

-Lasers can be helpful for patients with needle phobia, sclerosant allergy, or who are prone to telangiectatic matting.

Conclusion

Most of the studies performed in the last decade have focused on how to improve the resolution of vascular lesions that are resistant to traditional pulsed dye laser settings. These include efforts to investigate changes in wavelength, pulse duration, and fluency. Also more work has been done to investigate the IPL for use in refractory port wine stains and hemangiomas. Photodynamic therapy, alone or in conjunction with PDL has also been investigated. Also the use of adjunctive topical agents, such as imiquimod and rapamycin, offer interesting areas for further investigation.

Vascular lasers are playing an increasingly valuable role in the treatment of other conditions, such as psoriasis, warts, surgical scars (**Figures 8a, 8b**), striae, rhinophyma, acne, and Poikiloderma of Civatte or photodamaged skin. As more lasers are tried for various applications we will have more experience to report.

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Figure Legend

Table 1: Vascular wavelengths

532 nm	KTP
532 nm	Nd:YAG, frequency doubled
577-585 nm	Conventional PDL with pulse duration = .45ms
595 nm	Long-pulsed dye laser, pulse duration = 1.5ms
500-1200 nm	Noncoherent Intense Pulsed Light (IPL)
755 nm	Alexandrite
800, 810 nm	Diode
1064 nm	Long-pulsed Nd:Yag

Figure 1: Absorption spectra of hemoglobin

Figure 2a: Hemangioma of infancy on the nose, prior to treatment

Figure 2b: Same lesion 4 months later after 3 treatments of 595 nm PDL (courtesy of Jeffrey Poole, MD).

Figure 3a: Port wine stain (capillary malformation) of the chest, before treatment with PDL

Figure 3b: Same lesion following treatment with 595 nm PDL (Courtesy of Jeffrey Poole, MD).

Figure 4a: Segmental superficial ulcerating hemangioma of infancy on the leg, tender and painful prior to treatment

Figure 4b: Same lesion 10 months later after 6 treatments with 595 nm PDL(courtesy of Jeffrey Poole, MD).

Figure 5a: Proliferating superficial hemangioma of infancy, untreated

Figure 5b: Same lesion 10 months later after 4 treatments of 595 nm PDL

Figure 5c: Proliferating superficial HOI, after 21 months and 5 treatments of 595 nm PDL (courtesy of Jeffrey Poole, MD).

Figure 6a: Port wine stain of the V-2 distribution

Figure 6b: Same lesion following 9 treatments with the 595 nm PDL. Lesion was mostly resolved after 4 treatments (courtesy of Jeffrey Poole, MD).

Figure 7a: Facial telangiectasias of the chin, untreated

Figure 7b: Same facial telangiectasias after a single KTP 532 nm treatment (courtesy of Patricia Farris, MD).

Figure 8a: Surgical scar following male breast reduction, untreated

Figure 8b: Same scar after 4 treatments with PDL 595 nm, 1.5 ms at 5.5 J/cm^2 with 7mm spot size (courtesy of Marc Avram, MD)