Long-pulsed neodymium:yttrium-aluminum-garnet laser treatment for port-wine stains

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Objective: Laser treatment of port-wine stain (PWS) might be improved using a deeply penetrating wavelength.

Methods: PWSs in 17 patients were treated 3 times with a 595-nm pulsed dye laser (PDL) and a 1064-nm neodymium:yttrium-aluminum-garnet (Nd:YAG) laser. Fluences of 1.0, 0.8, and 0.6 times the minimum purpura dose (MPD) were used for Nd:YAG laser. Posttreatment biopsy specimens were taken. Blind assessment and quantitative analysis of PWS clearing were performed from digital photographs.

Results: MPD for Nd:YAG laser varied widely, from 40 to 250 J/cm^2. Purpura lasted longer after PDL. Treatment achieved similar 50% to 75% clearing with both PDL and Nd:YAG laser at 1 MPD. Nd:YAG caused greater perivascular and epidermal injury. Scarring occurred in the only patient treated with a Nd:YAG fluence greater than 1 MPD. Patients preferred Nd:YAG laser because of their faster recovery.

Conclusion: Nd:YAG laser used at MPD is as effective as PDL for treating PWS. Nd:YAG laser fluences higher than MPD may cause scarring. (J Am Acad Dermatol 2005;52:480-90.)

Port-wine stain (PWS) is a congenital microvascular malformation of the skin, occuring in 0.3% to 0.5% of newborns.[1,2] PWSs are present at birth and usually darken at puberty because of progressive dilation of the abnormal vessels.

Pulsed dye laser (PDL) is the standard treatment for PWS today. These treatments selectively damage superficial blood vessels. Almost all PWSs lighten after a series of PDL treatments, but most PWSs cannot be removed completely. The limited penetration depth of yellow light emitted by PDL may cause resistance to further PDL treatments; optical absorption and scattering in the epidermis and dermis limits penetration depth. Many PWS lesions extend 3- to 5-mm deep, but the effectiveness of the dye laser at 585 to 600 nm extends only about 1- to 2-mm deep.[3,4] The ratio of melanin to blood absorption is similar at 585 and 1064 nm, whereas the absolute values of absorption and scattering coefficients are considerably lower at 1064 nm as compared with 585 nm.[5] Therefore, deeper vessels may be selectively treated with 1064-nm pulses.[6,7] Clearing can probably be improved by using deeper penetrating light that selectively targets hemoglobin. The ratio of melanin to blood absorption is similar at 585 and 1064 nm, whereas the absolute values of absorption and scattering coefficients are considerably lower at

Abbreviations used:

B:	blue
G:	green
met-Hb:	met-hemoglobin
MPD:	minimum purpura dose
Nd:YAG:	neodymium:yttrium-aluminum-garnet
OD:	optical density
PDL:	pulsed dye laser
PWS:	port-wine stain
R:	reflectance
VAS:	visual analogue scale

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1064 nm as compared with 585 nm.[5] The absorption coefficient of blood at 1064 nm is 0.4/mm, which is much higher than that of the surrounding dermis (0.05/mm) at the same wavelength. This difference in absorption coefficients provides treatment selectivity of deep blood vessels.[6,7] Lower absolute values of blood absorption at 1064 nm may be compensated by increasing the fluence. The increase of the treatment fluence does not necessarily cause damage of epidermis, because the absolute absorption of melanin is lower at 1064 nm as well.

The objective of this pilot, open-label clinical study was to compare the efficacy and safety of a long-pulsed neodymium:yttrium-aluminum-garnet (Nd:YAG) laser with that of a standard PDL for treatment of PWSs. A fixed-fluence approach for Nd:YAG laser was abandoned after burn scarring occurred in the first patient treated. Effectiveness of Nd:YAG laser fluences near the threshold for immediate response (purpura) was then compared with PDL treatment at a standard treatment fluence. Lightening of PWS was assessed clinically and by analysis of digital photographs. Responses were compared in patients with pink, red, or purple PWSs, and with flat or hypertrophic PWSs.

METHODS

Patients

A total of 17 patients, age 18 to 52 years, skin types I to IV, with PWSs on different locations, measuring at least 5 cm^2 were included in the study. Pink, red, and purple PWSs with flat or hypertrophic regions were treated. In all, 11 were women and 6 were men. Patients who had any kind of PWS treatment within the last 2 months were excluded. Informed consent was obtained before enrollment in the institutional review board—approved study, conducted from January 2002 to March 2003.

Treatment

PWS in each patient was divided into 4 regions and treated 3 times at 1-month intervals. One region was treated using a 595-nm PDL (Scleroplus; Candela Corp, Wayland, Mass) (8 J/cm^2, 7-mm spot, 1.5 milliseconds) delivered with dynamic cooling (typically 30-millisecond spray duration), and the other 3 regions with a long-pulsed 1064-nm Nd:YAG laser (Modified Coolglide; Altus Medical, Inc, Brisbane Calif) (7-mm spot for fluences up to 100 J/cm^2, 5-mm spot for fluences above 100 J/cm^2; 3- to 15-millisecond pulse duration) with contact cooling. Randomization of the laser treatments was done on all 4 regions. Laser treatment parameters are shown in Table I. The PDL was used with approximately 10% pulse overlap, whereas nonoverlapping pulses were used in the regions treated with the Nd:YAG laser. The dynamic cryogen spray cooling device was used for the PDL. For the Nd:YAG laser, contact copper plate cooling in combination with bulk postcooling with ice packs was used. Ice packs were placed on the treated areas after delivering a series of 5 pulses with the Nd:YAG laser, and the cold packs were left on the treated areas while other areas were simultaneously being treated. Topical lidocaine 2.5% and prilocaine 2.5% cream (EMLA; Astra Pharmaceuticals, Wayne, Pa) was applied under occlusion for 1 hour before the treatment. Test exposures in the PWSs were done with Nd:YAG laser before each treatment. The test site was exposed in several rows to pulses with increasing fluences by 20% increments, starting at 30 J/cm^2. A series of 3 pulses on each row was administered until a minimum purpura dose (MPD) was determined. MPD was defined as the minimum fluence causing a subtle darkening (purpura) response lasting beyond 15 minutes after laser exposure in at least 2 of 3 test exposures. For each patient, MPD was used to determine the treatment fluences for the Nd:YAG laser, as shown in Table II (except for the first patient, who received treatment with fixed fluences and experienced scarring before changing the treatment protocol). The corresponding Nd:YAG fluences for the 3 treatment regions were individualized for each patient based on the determined MPD. The 3 Nd:YAG fluences were 1.0, 0.8, and 0.6 times the MPD. These fluences were used for all 3 treatments with the Nd:YAG laser. Mupirocin ointment (Bactroban, SmithKline Beecham; Mississauga, Ontario, Canada) was applied to the treated area for 3 to 4 days.

Table I. Comparison of both lasers used

	Nd:YAG	Pulsed dye
Device	Altus Coolglide	Candela Scleroplus
Skin cooling	Copper plate precooling, bulk postcooling with ice; cold gel	DCD 30/30
Wavelength, nm	1064	595
Spot size, mm	7; 5 (>100 J/cm^2)	7
Pulse width, ms	3-15	1.5
Fluence, J/cm^2	MPD, 0.8 MPD, 0.6 MPD	8
Pulse overlap	None	10%

DCD, Dynamic cooling device; *MPD*, minimum purpura dose; *Nd:YAG*, neodymium:yttrium-aluminum-garnet.

Treatment evaluation

Qualitative assessments. Blind assessments of treatment response in all 4 regions were made by

Table II. Patient details and neodymium:yttrium-aluminum-garnet minimum purpura doses

Age, y	PWS site	PWS color	Nd:YAG MPD		
			Fluence, J/cm^2	Pulse duration, ms	Spot size, mm
26	Cheek	Pink	75	6	7
29	Cheek	Red	60	7	7
18	Forearm	Purple	75	6	7
33	Cheek	Red	50	4	7
47	Neck	Dark purple	40	4	7
48	Back	Red	130	6	5
21	Cheek	Purple	40	4	7
49	Cheek	Dark purple	50	4	7
45	Cheek	Purple	75	6	7
28	Neck	Pink	90	8	7
24	Cheek	Purple	60	5	7
27	Lower aspect of back	Red	75	6	7
36	Forehead	Pink	90	6	7
52	Lower aspect of back	Red	130	8	5
33	Forehead	Purple	50	10	7
40	Thigh	Red	95	8	7

MPD, Minimum purpura dose; *Nd:YAG*, neodymium:yttrium-aluminum-garnet; *PWS*, port-wine stain.

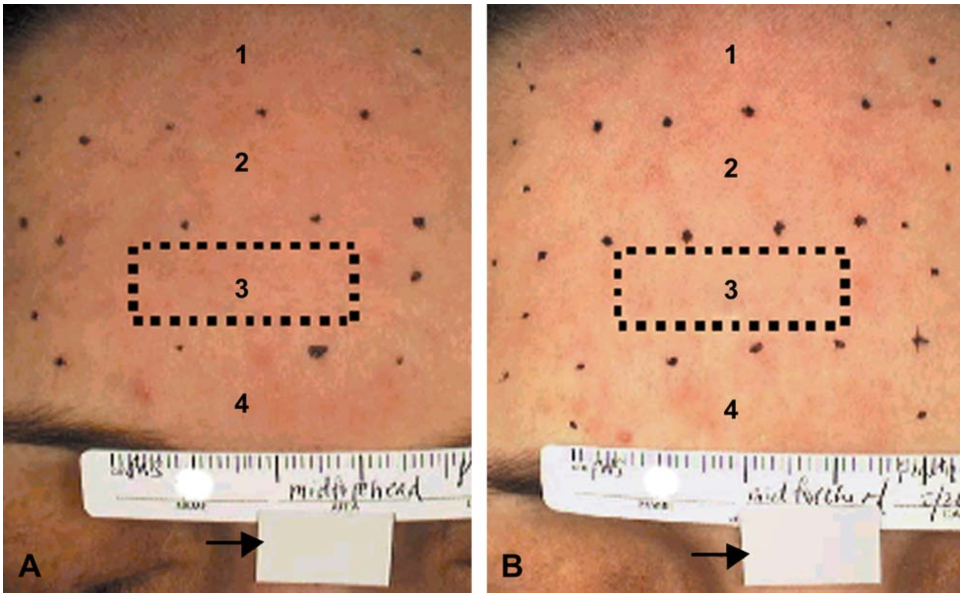

Fig 1. Quantitative evaluation of port-wine stain lightening using digital photography before (**A**) and after (**B**) 3 treatments. *1*, Neodymium:yttrium-aluminum-garnet (Nd:YAG) 60 J/cm^2; *2*, Nd:YAG 75 J/cm^2; *3*, Nd:YAG 90 J/cm^2; *4*, PDL 8 J/cm^2.

3 expert dermatologists from the digital photographs taken pretreatment (baseline) and 1 month after the last treatment. Apparent lightening of the lesion was given a score based on the following: 0 = 0%; 1 = 1% to 25%; 2 = 26% to 50%; 3 = 51% to 75%; and 4 = 76% to 100%. Adverse effects, including pigmentary changes and scarring after all 3 treatments, were recorded by the same investigator who performed the treatments.

A visual analogue scale (VAS), ranging from 0 to 10, was used in 16 patients for self-assessment of preference for Nd:YAG laser treatments compared with PDL. The same questionnaire was given on the 3 treatment visits and the final visit. The mean score for all 4 visits was obtained.

Quantitative assessment. An experimental approach for quantitative evaluation of PWS was done, using digital images taken before the first treatment and 1 month after the last treatment. Cross-polarized digital camera (Nikon E3s, Nikon Corp, Japan) images were analyzed in 4 patients with different PWS colors: pink, red, purple, and dark purple.

Cross-polarized photography was used to suppress the surface component of skin reflectance (R). A calibrated gray diffuse R standard, (approximately 55% R across the visible spectral range) attached to the skin within the frame of the image enabled absolute quantification of the PWS diffuse R in green (G) and blue (B) channels (Fig 1). For a given image, an average diffuse R and optical density (OD) of the PWS for the G and B channels were calculated using the following formulae:

$$R = PXL * R\ std/PXL\ std;\ OD = \log(1/R)$$

where PXL is average pixel value of the skin area of interest in the digital picture, PXL std is the average pixel value of the standard in the digital picture, and R std is 0.55 = diffuse R of the gray standard. Ratios of R and of OD between G and B image channels were used as measures of PWS darkness. Difference in the ratio before and after the series of treatments was used to measure individual PWS lightening of each treatment area. For each of the 4 treatment conditions, these differences were averaged to obtain mean response.

For the same patients, spectrophotometric measurements of the diffuse R spectra of the PWS were performed using a portable fiber-optic spectrophotometer with integrating sphere (Ocean Optics Inc, Dunedin, Fla) (Fig 2). An established spectrophotometric algorithm for quantifying blood content in tissue was used, as previously described.[8] The method is based on spectral analysis of diffuse R (λ) measured in the 400- to 750-nm wavelength range. Briefly, the algorithm is:

$$OD(\lambda) = \log[1/R(\lambda)],$$
$$E' = 100\,[OD_{\lambda 1} + 1.5(OD_{\lambda 2} + OD_{\lambda 3}) - 2.0(OD_{\lambda 4} + OD_{\lambda 5})],$$
$$M = (\langle OD \rangle_{645-655} - \langle OD \rangle_{695-705}),$$
$$E = E'\,(1 + 0.05\,M)$$

where OD (λ) is spectrally resolved OD, M is an index of skin melanin content, E is an index of skin blood content, $\langle OD \rangle_{645-655}$ and $\langle OD \rangle_{695-705}$ are the average of OD from 645 to 655 nm, and from 695 to 705 nm, respectively, and λ_1 = 560 nm, λ_2 = 543 nm, λ_3 = 576 nm, λ_4 = 510 nm, and λ_5 = 610 nm.

The difference in E determined before the treatments and 1 month after the last treatment were calculated and used to assess lightening of the PWS in each of the 4 treatment areas. The results yielded by quantitative digital photography, spectrophotometry, and blind assessment of treatment response by 3 expert dermatologists were compared.

Histology

All the patients enrolled in the study were given the option to allow the investigators to take a skin biopsy specimen. The biopsy specimens were taken within 5 minutes of laser exposures. The investigators determined the MPD for PDL exposures only on this subset of 4 patients consenting to biopsies, to make a histologic comparison of the Nd:YAG at MPD and the PDL at MPD. Local anesthesia with 1% lidocaine was injected before each biopsy. The biopsy sites were sutured, and mupirocin ointment applied daily for 7 to 14 days before suture removal. The specimens were fixed in 10% buffered formalin, processed in paraffin, stained with hematoxylin and eosin, and blindly evaluated by a dermatopathologist. Depth of microvascular damage was measured using an ocular micrometer (Zeiss, Oberkochen, Germany) from the dermoepidermal junction to the deepest dermal vessel showing vessel wall necrosis. Epidermal and dermal changes were also noted if present.

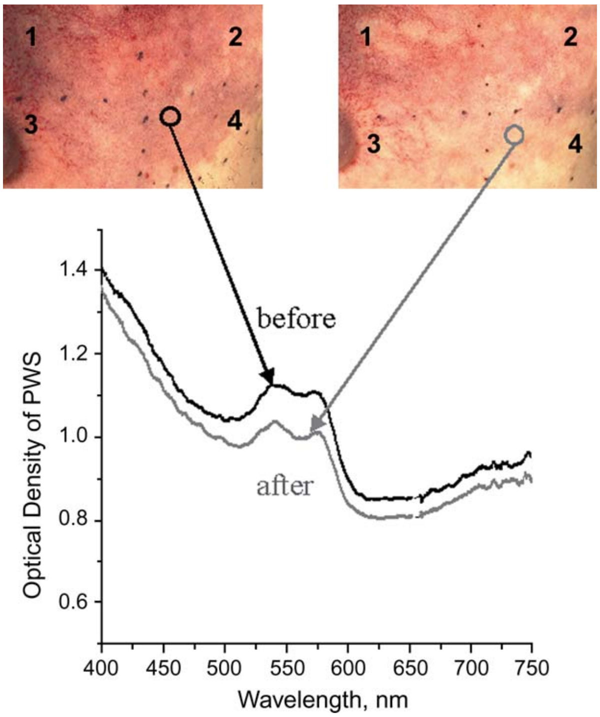

Fig 2. Quantitative evaluation of port-wine stain (PWS) lightening using spectrophotometry before and after 3 treatments. *1*, Neodymium:yttrium-aluminum-garnet (Nd:YAG) 40 J/cm^2; *2*, Nd:YAG 50 J/cm^2; *3*, Nd:YAG 60 J/cm^2; *4*, PDL 8 J/cm^2.

Statistical analysis

Mann-Whitney test ($P < .05$) was performed on the mean lightening scores after each of the 4 laser treatments and the Wilcoxon test ($P < .05$) was used to analyze the patients' mean VAS scores.

Table III. Mean lightening scores, digital photography pixel values, and relative erythema indices after 3 laser treatments

	PDL				Nd:YAG, MPD			Nd:YAG, 0.8MPD			Nd:YAG, 0.6 MPD		
Age, y	**PWS color**	**MLS**	**DPH**	**REI ± SD**	**MLS**	**DPH**	**REI ± SD**	**MLS**	**DPH**	**REI ± SD**	**MLS**	**DPH**	**REI ± SD**
26	Pink	2.67			0.67			1			2		
29	Red	3.67			3.33			2.67			2.33		
18	Purple	2.67			0.67			1			1.67		
33	Red	3.33	14.7	15 ± 1.7	2.33	7.8	7.3 ± 0.9	2	4.9	5.2 ± 0.9	2	4.8	4.3 ± 2.12
47	Dark purple	2			2			1.67			2		
48	Red	3.33			2.67			1.67			2		
21	Purple	1.67			1.67			1			1.67		
49	Dark purple	1.67	3.5	4.1 ± 0.5	3	6.3	6.8 ± 1.9	1	3.2	4.2 ± 0.7	2	4.8	5.1 ± 1.2
45	Purple	2			0.67			1.33			1		
28	Pink	3.33			1.33			0.67			1.33		
24	Purple	3.67	12	11 ± 2.1	3.67	12.4	11.5 ± 1.5	2.33	8.9	8.1 ± 1.2	2	4.5	4.8 ± 1.9
27	Red	2.33			1.33			1.33			1.67		
36	Pink	2.33	5.5	7.3 ± 2.1	3.33	6.5	8.2 ± 0.7	2.67	5	6.5 ± 0.9	0.67	1	2.1 ± 0.7
52	Red	3			2			1.33			2.33		
33	Purple	4			3			2			2		
40	Red	1.33			1			1			1		

DPH, Digital photography; *MLS*, mean lightening score; *MPD*, minimum purpura dose; *Nd:YAG*, neodymium:yttrium-aluminum-garnet; *PDL*, pulsed dye laser; *PWS*, port-wine stain; *REI*, relative erythema index averaged over 3 measurements.
0 = 0%; 1 = 1%-25%; 2 = 26%-50%; 3 = 51%-75%; 4 = 76%-100%.

RESULTS

Treatment responses

Of the 17 patients, 16 completed all 3 laser treatments. One patient, who was the first entered in the study, received only one treatment. The Nd:YAG laser exposures in this patient were based on an original dosing protocol using 3 fixed fluences (7-mm spot; 4- to 8-millisecond pulse duration; 50 J/cm^2, 75 J/cm^2, and 100 J/cm^2). The first fluence was below his MPD of 60 J/cm^2, whereas the two higher doses were at $1.2\times$ and $1.7\times$ above MPD. Deep dermal photocoagulation with relative sparing of the papillary dermis occurred with the higher fluence in this patient, resulting in a scar. The dosimetry protocol for Nd:YAG laser exposures was then changed to be based on individual patient MPD instead of fixed fluences, as described. Data for the other 16 patients were used for the analysis of PWS response.

As judged by the 3 expert dermatologist on PDL-treated regions, 3 patients (19%) had more than 75% clearing of the PWS lesion, 6 (38%) had 51% to 75% clearance, 6 (38%) had 26% to 50% clearance, and one patient (6%) had 25% or less clearance. On the Nd:YAG regions treated at 1 MPD, 1 patient (6%) had more than 75% clearing of the lesion, 5 (31%) had 51% to 75% clearance, 4 (25%) had 26% to 50% clearance, and 6 (38%) had clearance of 25% or less. On the Nd:YAG regions treated at 0.8 MPD, two patients (13%) had 51% to 75% clearance, 5 (31%) had 26% to 50% clearance, and 9 (56%) had a clearance of 25% or less. On the Nd:YAG regions treated at 0.6 MPD, 12 patients (75%) had 26% to 50% clearance, and 4 (25%) had 25% or less clearance in the PWS treatment sites (Table III). There was no significant difference in the mean lightening scores between the PDL and the Nd:YAG regions treated at 1 MPD ($P > .05$) (Fig 3). There was significantly greater clearance after 3 treatments with the PDL compared with the lower fluences of Nd:YAG laser (ie, 0.8 and 0.6 MPD; $P < .05$). Similarly, the mean lightening scores after Nd:YAG treatment at 1 MPD were significantly higher than those after 0.8 and 0.6 MPD ($P < .05$). Representative photos are shown in Figs 4 and 5. The results yielded by quantitative digital photography and spectrophotometry on the 4 patients examined were consistent with the mean lightening scores as graded by the 3 blinded, expert dermatologists (Table III).

Of the patients, 3 had pink (light-colored) PWSs. Two of these had greater mean lightening scores after PDL, whereas one responded better to Nd:YAG at 1 MPD. In all, 6 patients had red (moderately dark) PWSs. In all 6, response to PDL was better than response to Nd:YAG laser at 1 MPD. A total of 5 patients had purple (dark-colored) PWSs. Of these, 3 had greater lightening after PDL than after Nd:YAG laser at 1 MPD, whereas two demonstrated equal response to both lasers. Two patients had dark purple, hypertrophic PWS. Of these, one showed a greater mean lightening score after the Nd:YAG laser at 1 MPD, and the other had an equal response to both PDL and Nd:YAG at 1 MPD. Of the two patients with hypertrophic PWSs, both showed decreased lesion thickness after Nd:YAG laser treatment.

Nd:YAG MPD

MPD values for the Nd:YAG laser varied widely among patients, and were lower in darker PWSs. Variation was greatest in the group with pink PWSs. The MPD for pink PWSs ranged from 90 to 250 J/cm^2, delivered with 6- to 15-millisecond pulses, at 7- and 5-mm spot sizes for fluences up to 100 J/cm^2 and above 100 J/cm^2, respectively. For red PWSs, the Nd:YAG laser MPD ranged from 50 to 130 J/cm^2, delivered with 4- to 8-millisecond pulses at 7- and 5-mm spot sizes for fluences below and above 100 J/cm^2, respectively. The MPD for the purple PWSs ranged from only 40 to 60 J/cm^2, delivered with 4-millisecond pulses and a spot size of 7 mm (Table IV).

Adverse effects

The first patient entered into this study, and the only one to receive Nd:YAG laser fluence greater than 1 MPD, developed a hypertrophic scar on the back of his neck (Fig 6) on regions treated at 1.2 and 1.7 MPD. Two patients (12%) developed postinflammatory hyperpigmentation in the PDL-treated sites only, which resolved spontaneously in 4 to 6 months. One other patient (5%) developed a pyogenic granuloma, appearing 1 week after the first PDL treatment. This was biopsied to confirm its diagnosis (Table V).

Gross and microscopic findings

Purpura from the Nd:YAG at MPD was a subtle dusky purple color, appearing immediately after laser irradiation. In contrast, purpura after PDL was a red hemorrhagic purpura, taking up to a few minutes to become visible.

Histologic comparison of skin sites exposed to Nd:YAG at 1- and 1.2-MPD fluence was done in 5 patients to examine the setting under which the first patient developed scarring after 1.2 MPD. At 1.2 MPD, epidermal necrosis was noted in 4 of 5 specimens. At 1 MPD, epidermal necrosis was absent, with the exception of one specimen that showed partial keratinocyte elongations typical for thermal injury. At both 1 and 1.2 MPD, there was microvascular coagulation necrosis, with an intravascular coagulum and perivascular collagen denaturation. Dermal collagen damage after Nd:YAG laser at 1.2 MPD was not only confined around the blood vessels; diffuse thermal necrosis was noted extending as far as the reticular dermis, with relatively less injury in the papillary dermis. In some specimens, thermal necrosis of the dermis extended to the subcutaneous region. Fig 7 shows a comparison of the gross tissue morphology and microscopic picture of an Nd:YAG-treated PWS at MPD and 1.2 MPD. Although the degree of dermal injury was much greater at 1.2 MPD, apparently the depth of vascular injury was not any deeper. Mean depth of the deepest vascular damage on the 5 patients studied histologically after Nd:YAG at MPD and 1.2 MPD was 1.95 mm and 2.0 mm, respectively.

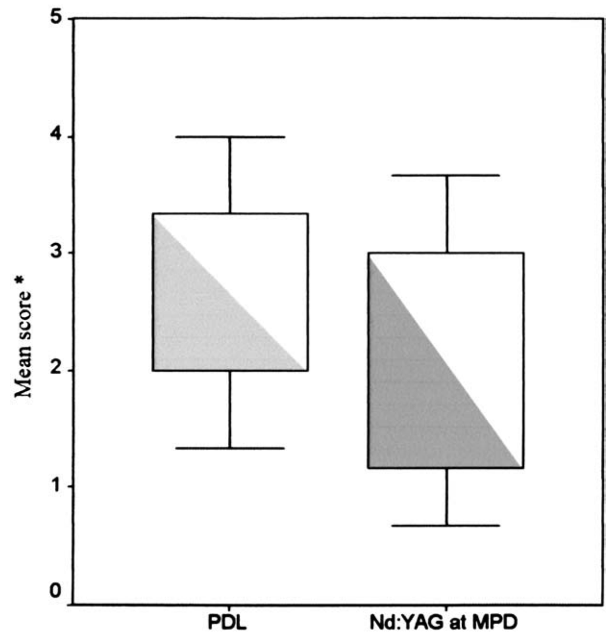

Fig 3. Mean lightening scores of port-wine stain after 3 treatments with pulsed dye laser (*PDL*) and neodymium: yttrium-aluminum-garnet (*Nd:YAG*) at minimum purpura dose (*MPD*). *Mean lightening score: 0 = 0%; 1 = 1% to 25%; 2 = 26% to 50%; 3 = 51% to 75%; and 4 = 76% to 100%.

In 4 patients biopsied on sites irradiated with both the Nd:YAG and PDL lasers at 1 MPD, epidermal necrosis was evident in 3 treated with the Nd:YAG at MPD. No epidermal damage was apparent in the PDL sites. Photocoagulation of blood vessels was deeper with the Nd:YAG than with PDL. Mean depth of the deepest vessel damage for Nd:YAG and PDL was 2.6 mm and 0.95 mm, respectively, a factor of 2.7 times. Fig 8 compares the histology of a PWS exposed to the Nd:YAG at MPD and the PDL at 8 J/cm^2.

Patient satisfaction

The mean VAS score for the Nd:YAG at MPD was significantly higher than the VAS score for the PDL-treated region at 5.84 and 4.85, respectively ($P < .05$). Patients preferred the Nd:YAG laser because of its shorter recovery period and comparable results

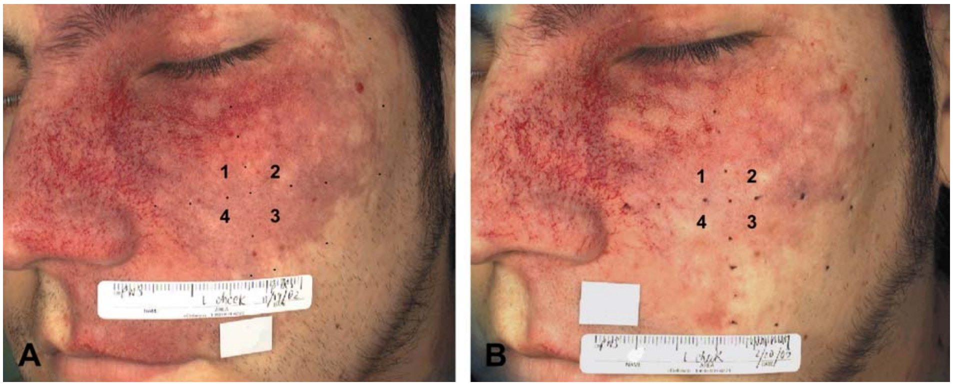

Fig 4. Port-wine stain on left cheek before (**A**) and after (**B**) 3 treatments. *1*, Neodymium:yttrium-aluminum-garnet (Nd:YAG) 40 J/cm^2; *2*, Nd:YAG 50 J/cm^2; *3*, Nd:YAG 60 J/cm^2; *4*, PDL 8 J/cm^2.

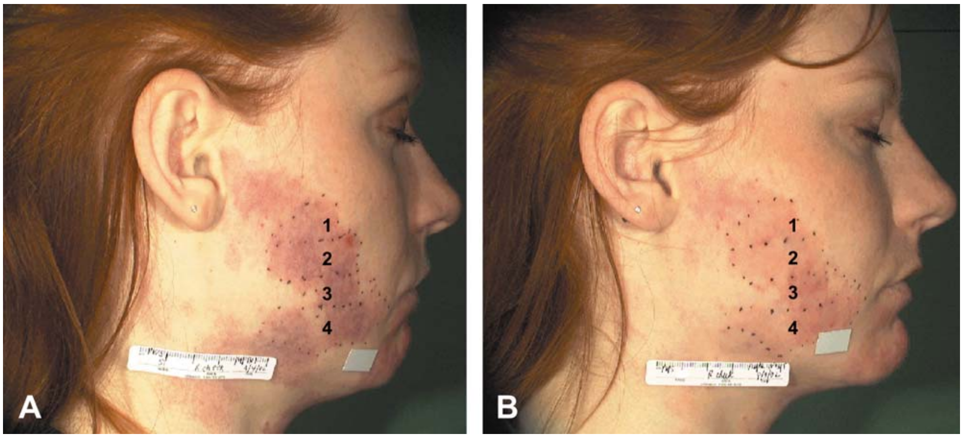

Fig 5. Port-wine stain on right cheek before (**A**) and after (**B**) 3 treatments. *1*, Neodymium:yttrium-aluminum-garnet (Nd:YAG) 60 J/cm^2; *2*, PDL 8 J/cm^2; *3*, Nd:YAG 40 J/cm^2; *4*, Nd:YAG 50 J/cm^2.

Table IV. Neodymium:yttrium-aluminum-garnet minimum purpura dose for all patients

	Nd:YAG MPD		
PWS color	Fluence, J/cm^2	Pulse duration, ms	Spot size, mm*
Pink	90-250	6-15	5, 7
Red	50-130	4-8	5, 7
Purple	40-60	4	7

MPD, Minimum purpura dose; *Nd:YAG*, neodymium:yttrium-aluminum-garnet; *PWS*, port-wine stain.
*A 7-mm spot for fluences ≤ 100 J/cm^2, 5-mm spot for fluences>100 J/cm^2.

with PDL. Purpura after Nd:YAG laser treatment lasted for 3 days, whereas purpura in the PDL-treated site was darker and lasted for 7 to 10 days.

DISCUSSION

This is the first study to treat PWSs with a long-pulsed 1064-nm Nd:YAG laser and compare the results with standard PDL treatment. As expected, we found that selective photothermolysis of microvessels in PWS can be achieved at much greater depth by 1064-nm Nd:YAG laser pulses. We also found a large variation in the Nd:YAG laser fluence tolerated among individual PWS lesions. When delivered at the immediate response threshold fluence of 1 MPD, red and purple PWSs lightened over a series of 3 treatments equally well with Nd:YAG and PDL. No significant difference was found in the mean lightening scores between PDL and Nd:YAG laser delivered at 1 MPD. Patients preferred Nd:YAG laser treatment at 1 MPD to standard PDL treatment by self-assessment, because of decreased purpura.

In this study, careful observation of the immediate response threshold was necessary as an end point to individualize treatment fluence for PWS lesions, using the long-pulsed Nd:YAG laser. When performed at 1 MPD, treatment was safe and effective,

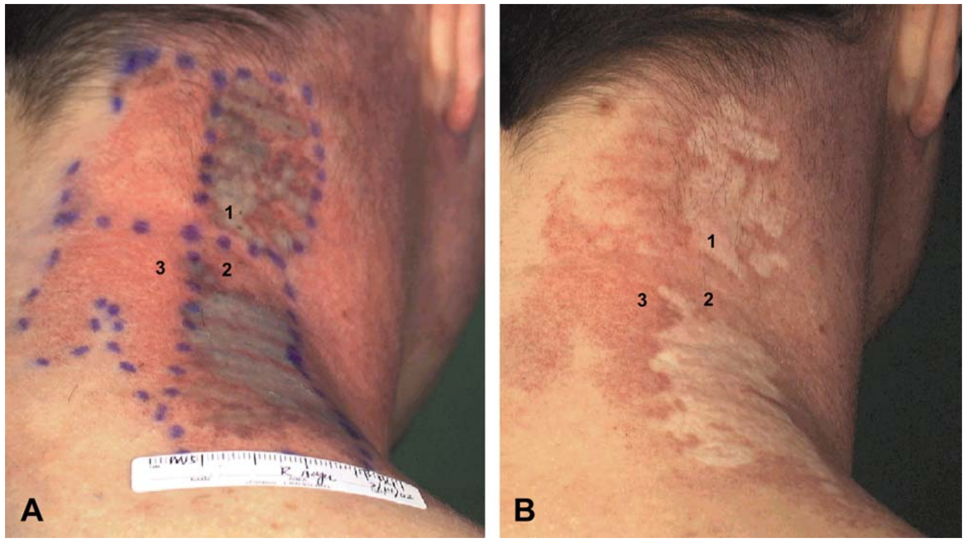

Fig 6. Hypertrophic scarring on back of right side of neck from neodymium:yttrium-aluminum-garnet (Nd:YAG) laser treatment. **A**, Immediately after treatment with Nd:YAG laser. Regions *1* and *2* demonstrating grayish discoloration on treatment areas at 50 J/cm^2 and Nd:YAG 75 J/cm^2, respectively. Region *3* treated with Nd:YAG at 50 J/cm^2 showing no purpura posttreatment. **B**, Hypertrophic scarring on neck 1 year posttreatment.

with histologic confinement of thermal injury to dermal blood vessels. The anatomic depth of Nd:YAG laser treatment was greater than the depth of PDL treatment. However, at a fluence of just 1.2 MPD, thermal damage after Nd:YAG laser treatment extended to the dermis between vessels. The first patient entered in the study was treated based on the original protocol with 3 fixed Nd:YAG laser fluences (50, 75, and 100 J/cm^2) corresponding in this particular patient to 0.8, 1.2, and 1.7 MPD. At the two higher fluences, grayish discoloration somewhat darker than the threshold (MPD) response was noted immediately. A burn eschar and scarring resulted after treatment at 1.2 and 1.7 MPD. We concluded that PWS response to Nd:YAG laser treatment at fluences greater than MPD exhibits a very steep increase in treatment response. It is, therefore, important to properly determine the MPD when using long-pulsed Nd:YAG laser to treat PWS. Skin cooling also plays an important role in limiting the dermal injury. Besides the copper plate precooling available in the long-pulsed Nd:YAG laser, bulk postcooling with ice was used during treatments in this study. In contrast, it is well established that PDL treatment of PWS can be performed safely at twice the purpura threshold fluence, even without active skin cooling. It should also be noted that skin cooling by the contact method used with the Nd:YAG laser in this study can vary widely with technique, as compared with the automated dynamic cooling device of the PDL.

Table V. Adverse reactions noted on the neodymium:yttrium-aluminum-garnet and pulsed dye laser

Adverse effects	Nd:YAG (n = 17)*	PDL (n = 17)*
Hyperpigmentation	0	2 (12%)
Hypopigmentation	0	0
Hypertrophic scar	1(5%)	0
Pyogenic granuloma	0	1 (5%)

Nd:YAG, Neodymium:yttrium-aluminum-garnet; *PDL*, pulsed dye laser.
*All 17 patients are included in the adverse reactions, including the first patient who did not complete the study.

The steep fluence-response curve of Nd:YAG laser treatment may be caused by several phenomena. When blood is heated to 50 to 54°C, partial oxidation of oxyhemoglobin leads to met-hemoglobin (met-Hb) formation.[9,10] Optical absorption by met-Hb in the near infrared spectral range is much higher than that of either hemoglobin or oxyhemoglobin.[11,12] Several in vitro studies[13,14] have demonstrated that when blood is photocoagulated by 1064-nm Nd:YAG laser pulses, absorption at 1064 nm increases on the millisecond time scale by a factor of about 3, which can be explained by partial conversion of oxyhemoglobin to met-Hb. Formation of a coagulum is also accompanied by loss of water from lumen blood, resulting in concentration of chromophores. Optical scattering also increases in thermally coagulated blood. Black et al[15] reported

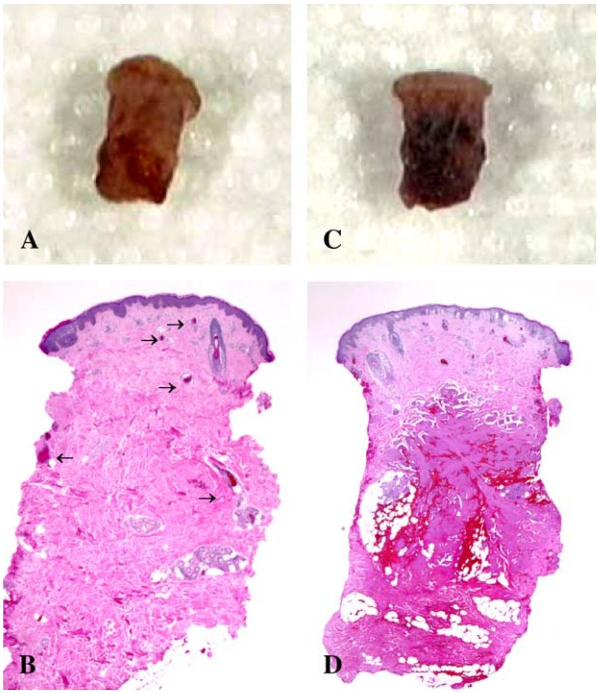

Fig 7. Gross and histologic pictures of neodymium:yttrium-aluminum-garnet (Nd:YAG)—treated port-wine stain (PWS) at minimum purpura dose (MPD) and 1.2× MPD. PWS treated with Nd:YAG at MPD: 130 J/cm^2, 6 milliseconds, 5-mm spot. **A**, Tissue sample taken 10 minutes after laser irradiation. Note coagulated blood in dermis. **B**, Intravascular coagulum noted in some superficial blood vessels, but mostly affecting blood vessels located in mid to lower reticular dermis (*arrows*). PWS treated at 1.2× MPD: 155 J/cm^2, 7 milliseconds, 5-mm spot. **C**, Gross thermal damage noted in mid to lower dermis. **D**, Epidermal necrosis with thermal necrosis on mid to lower reticular dermis, extending to subcutaneous region. Red blood cells thermally denatured, with larger vessels preferentially involved. Perivascular collagen denaturation noted. (**B** and **D**, Hematoxylin-eosin stain; original magnifications: **B**, ×25; **D**, ×25.)

that photocoagulation of human blood results in increased absorption by a factor of 2 to 10 and increased scattering by a factor of 2 to 4 in the wavelength range from 500 to 1100 nm. Our results in this human study are consistent with a significant increase of absorption during 1064-nm Nd:YAG laser pulses at fluences greater than MPD.

Another important parameter that may affect laser treatment is the volume fraction of dermis occupied by PWS vessels, which ranges from less than 0.05 in pink PWSs to about 0.25 in dark purple, hypertrophic PWS lesions. During laser irradiation, bulk heating of the dermis depends on the total energy absorbed per unit dermal volume, related to both the peak temperature and the collective density of target vessels.[16] The importance of bulk dermal heating may be greater for Nd:YAG laser than for PDL because 1064 nm penetrates deeper than 585 nm. The wide range of MPD noted with the Nd:YAG laser among patients in this study (40-250 J/cm^2) is consistent with this hypothesis. Also consistent is the variation of MPD with lesion color. The MPD for pink PWSs ranged from 90 to 250 J/cm^2, whereas MPD for purple PWSs ranged from 40 to 60 J/cm^2.

With the exception of the first patient, who had a burn scar after Nd:YAG laser treatment performed above the MPD, side effects were minimal. On the PDL-treated regions, 2 of 16 (12%) patients developed hyperpigmentation that resolved spontaneously in 4 to 6 months. This is typical for PDL treatment of PWSs, consisting of hemosiderin deposition and/or postinflammatory melanin pigmentation. One of the 16 patients (7%) developed a pyogenic granuloma after the first PDL treatment. Although not commonly reported, pyogenic granulomas after PDL treatment have been noted.[17-19]

An interesting observation regarding two patients during treatment with Nd:YAG laser on the side of the neck is the induction of involuntary motor twitching of the ipsilateral forearm. Anecdotally, we have also witnessed similar twitching foot dorsiflexion for patients during 1064- and 810-nm near infrared laser treatment of the side of the knee area during hair removal. It appears that near infrared laser pulses at high fluences are able to stimulate motor nerve action potentials, a hypothesis that may deserve further study.

Cross-polarized color digital photography was used in this study for documentation and qualitative blind assessment of PWS lightening. A simple quantitative method was tested in this study, using relative changes in ratio of G and B image channel pixel values that were calibrated to the diffuse R of a known standard label placed on the skin. This inexpensive method mimics more complex spectrophotometric measurements, and correlated well in this study with blind assessments of PWS lightening. Standardization of the method, presented here for interest, is necessary.

In summary, this study shows that an Nd:YAG laser emitting pulses in the 3- to 15-millisecond region and used at the threshold fluence for subtle, immediate purpura (ie, at 1 MPD), is safe and as effective as PDL for treating PWS lesions. Patients preferred the Nd:YAG laser over PDL, based on self-assessment using a VAS tool, because of less purpura. Histologically, Nd:YAG laser targets PWS vessels much deeper than PDL. Clinically, caution is needed when using Nd:YAG laser to treat PWSs, because skin response changes rapidly at fluences greater than MPD, and MPD varies widely among different PWS

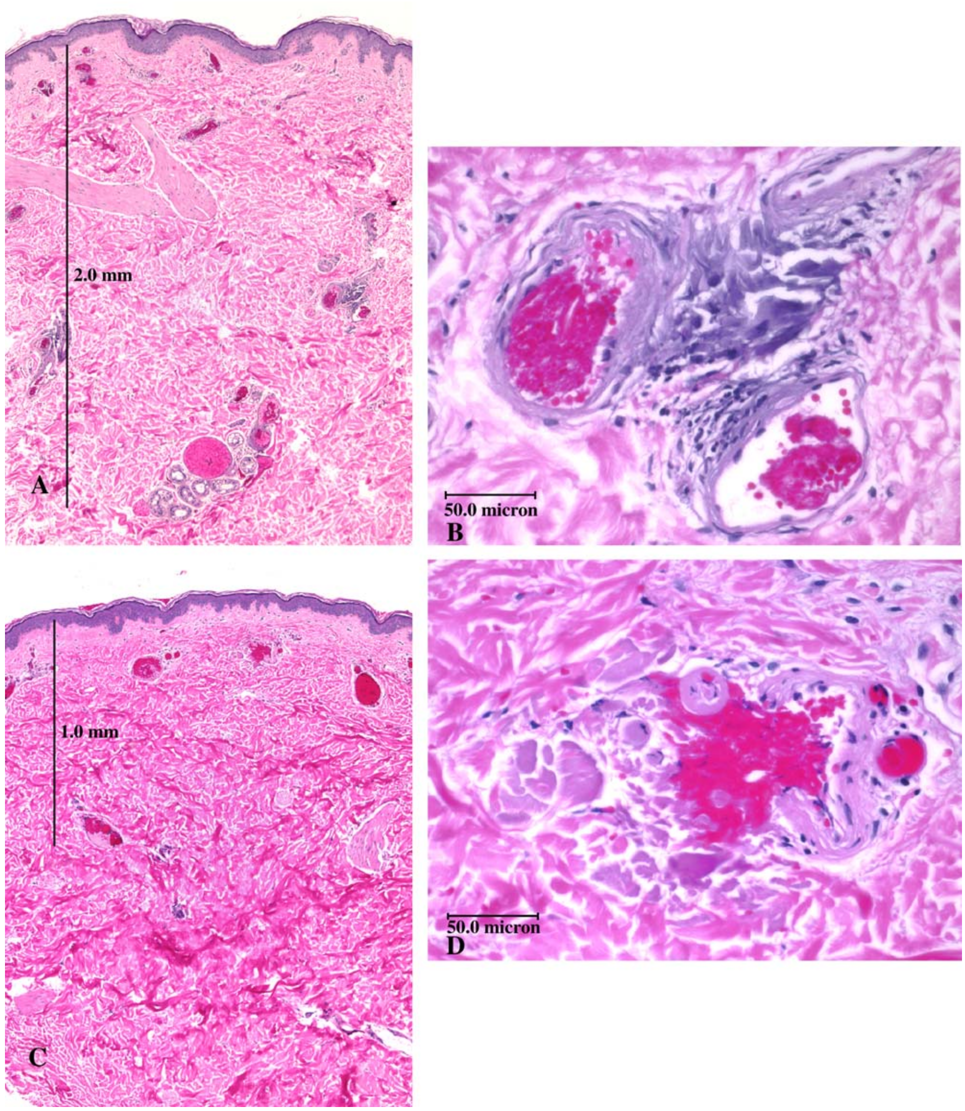

Fig 8. Histologic pictures of neodymium:yttrium-aluminum-garnet (Nd:YAG)-treated port-wine stain (PWS) at minimum purpura dose (MPD) and pulsed dye laser (PDL) at 8 J/cm^2. Tissue samples were taken 10 minutes after laser irradiation. **A**, PWS treated with Nd:YAG at MPD: 130 J/cm^2, 6 milliseconds, 5-mm spot. Deepest vessel damage was at 2 mm from dermoepidermal junction (DEJ). **B**, Close-up view of blood vessel wall from *A* at ×400, showing intravascular coagulum formation with perivascular collagen denaturation. **C**, PWS treated with PDL at 8 J/cm^2, 1.5 milliseconds, 7-mm spot, with dynamic cooling. Deepest vessel damage extended up to 1 mm below DEJ. **D**, Higher magnification of *C* (×400) showing ruptured blood vessel wall and hemorrhage. Note collagen denaturation around blood vessel wall. (**A** to **D**, Hematoxylin-eosin stain; original magnifications: **A** and **C**, ×50; **B** and **D**, ×400.)

lesions. It is important to note that there are several long-pulsed 1064-nm lasers on the market, with somewhat different pulse width, fluence, spot size, and skin-cooling systems. In this study, we randomized laser treatment sites. Different regions of the body may have inherent differences in the response to laser treatment. Future studies are required to compare treatment effects of the long-pulsed Nd:YAG versus the PDL on the same body site. The results of our study suggest that determining MPD with the particular Nd:YAG laser being used on a given body site, then treating at or below MPD, is a rational clinical approach. Potentially, improvements such as limited dermal injury by using bulk skin precooling, and/or feedback control to detect formation of met-Hb during the laser pulses, may improve the safety of Nd:YAG lasers for treating PWSs.

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