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Pulsed Dye Laser Treatment of Port-Wine Stains in Infancy Without the Need for General Anesthesia

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IMPORTANCE Recent concerns regarding repetitive use of general anesthesia in children younger than 3 years have placed greater importance on the controversy surrounding the timing of the initiation of port-wine stain (PWS) laser treatment.

OBJECTIVE To evaluate the use of PWS treatments at the age of 1 year or younger in the office setting without general anesthesia.

DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort study based on medical record reviews at a single, high-volume laser center for children who started pulsed dye laser treatment at the age of 1 year or younger for their PWS between 2000 and 2017. The data cutoff was at 1 year after the initial treatment to have comparable data points.

MAIN OUTCOMES AND MEASURES The primary outcome was improvement of PWSs using before and after photographs, which were reviewed by 4 physicians independently and graded using the following 5-point visual analog scale (VAS): poor (grade 1: 0%-25% improvement), fair (grade 2: 26%-50% improvement), good (grade 3: 51%-75% improvement), excellent (grade 4: 76%-99% improvement), and complete (grade 5: 100% improvement) clearance.

RESULTS Of the 197 patients (73 [37.1%] boys; 124 [62.9%] girls), most (149 [75.6%]) had facial lesions. The mean age at the time of first treatment was 3.38 months (range, 5-355 days) and the mean number of treatments was 9.8 (range, 2-23; median, 10). Per the mean physician VAS grading of 197 patients, 51 patients (25.9%) showed 100% clearance (mean [range] VAS score of 4.78 [4.5 – 5]); 81 patients (41.1%) showed 76 to 99% improvement (mean [range] VAS score of 3.91 [3.5 to <4.5]); 44 patients (22.3%) showed 51% to 75% improvement (mean [range] VAS score of 2.86 [2.5 to <3.5]); 13 patients (6.6%) showed 26% to 50% improvement (mean [range] VAS score of 2.12 [1.5 to <2.5]); and 8 patients (4.1%) showed 0 to 25% improvement (mean [range] VAS score of 0.78 [0 to <1.5]). The presence of a V1 (first branch of the trigeminal nerve [ophthalmic nerve]) lesion was associated with a statistically significantly higher clearance rate by a VAS grade of 0.55 (95% CI, 0.25-0.84; $P < .001$). The mean (SD) VAS grade for all patients was 3.65 (1.26), corresponding to excellent clearance. None of the patients experienced scarring or permanent pigmentary change.

CONCLUSIONS AND RELEVANCE In this study, treatment of PWSs in infancy was both safe and effective. Early intervention allows for treatment without general anesthesia, maximizing the chance to achieve clearance before school age and thereby minimizing the negative outcome of PWSs for both the patient and the family.

Editorial

Video

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A recent US Food and Drug Administration warning[1] has raised awareness regarding concerns about repeated use of general anesthetic and sedation drugs in children younger than 3 years.[2] Although the warning has been debated owing to some studies supporting the concern[3] and others not supporting it,[4] raised awareness of the topic has placed greater importance on the already controversial topic of when to initiate port-wine stain (PWS) therapy in pediatric patients, which requires repeated treatments often performed with general anesthesia.

Port-wine stains are capillary malformations that affect up to 0.5% of newborns.[5,6] A PWS usually starts as an erythematous patch that grows with the child and tends to darken and thicken over time.[7,8] The development of the pulsed dye laser (PDL), which targets the hemoglobin of the PWS vessels, has allowed for effective treatment of PWSs over the years since it was first reported in 1988.[9] Treating PWSs during infancy allows for treatment without general anesthesia as it is easier to hold the patient still during the treatment. Uncooperative older children are more challenging to keep immobilized during laser treatment, and many receive PWS treatments under general anesthesia. Despite the benefits of early treatment, many physicians hesitate to treat PWSs during infancy and especially are wary of treating them in an office setting without anesthesia. Given our positive clinical experience, we designed a retrospective study to evaluate PWS treatments in infants 1 year or younger in the office setting without general anesthesia.

Key Points

Question Is it safe and effective to initiate port-wine stain laser treatments without general anesthesia in infancy?

Findings In this retrospective analysis of 197 infants with port-wine stains who began laser treatment during infancy, 34.0% of the patients achieved 100% clearance and 37.6% showed 76% to 99% improvement. On average, patients appeared to achieve excellent clearance, and none of the patients experienced scarring or permanent pigmentary change.

Meaning The findings of this study suggest that treatment of port-wine stains in infancy is both safe and effective, allowing for treatment without general anesthesia and successful therapeutic outcome.

Methods

A medical records review of patients who started treatment for PWSs between 2000 and 2017 at 1 year or younger was performed. To have comparable data points, the data cutoff was set at 1 year after the initial treatment. Those who did not have follow-up photographs for evaluation were excluded. Lesions suggestive of nevus simplex (eg, midline stains) were also excluded. The treatments were performed using a 595-nm PDL (Vbeam Perfecta; Syneron Candela) without topical or general anesthesia. For the lesions involving the periocular region, stainless steel corneal shields were placed after application of an anesthetic solution before the treatments to provide protection (**Video**). The study was approved by Asentral Institutional Review Board with waiver of informed consent.

Relevant data, including demographic information, age at the time of the procedure, lesion size, location, laser settings, and treatment dates, were extracted from the records. The clinical photographs taken at the initial treatment visits (N=394) were compiled as before photos. The clinical photographs taken at the latest visit in the 1-year cutoff window (1 year after the initial treatment) were compiled as after photos. Before and after photographs for each patient were then compiled side by side for grading. Although there is not a validated scoring scale available for PWSs, a visual analog scale (VAS) has been used in other dermatologic studies to evaluate treatment success based on clinical improvement. The photographs were independently reviewed and graded by 4 physicians (H.J., L.J.B., D.A.B., and R.G.G.), using the following VAS: poor (grade 1: 0%-25% improvement), fair (grade 2: 26%-50% improvement), good (grade 3: 51%-75% improvement), excellent (grade 4: 76%-99% improvement), and complete (grade 5: 100% improvement) clearance. The photographs were also reviewed for any apparent complications.

Statistical Analysis

Our statistical analysis was performed by running both an unpaired, 1-tailed *t* test and multiple linear regression analysis, in which $\alpha = .05$. Matlab, version 2018b software (MathWorks) was used to conduct the analysis. An unpaired, 2-tailed *t* test was performed to analyze the demographic and lesion-specific variables that affected treatment outcomes.

Results

A total of 197 patients (73 [37.1%] boys and 124 [62.9%] girls) were included in the study (**Table 1**). Most of the patients (179 [90.9%]) had Fitzpatrick skin types I to III (light). Sixteen patients (8.1%) had skin type IV (medium brown) and 2 patients (1.0%) had skin types V to VI (dark). Most of the lesions (149 [75.6%]) were located on the face, with the rest located on the trunk or extremities. Lesions in both areas received a mean (SD) VAS grading of 3.65 (1.26), without any significant complication. Eighty-one of the 197 patients (41.1%) had periocular involvement. The lesion size ranged from 0.49 to 600 cm^2 (mean, 61.09). Treatment settings using the PDL were 10 to 12 mm, 6.5 to 9.0 J/cm^2, and 0.45 to 1.5 milliseconds. However, settings varied based on lesion location. The initial settings chosen for the face and neck lesions were 10-mm spot size, 8.0 to 9.0 J/cm^2, and 1.5 milliseconds. For the body lesions, the typical initial settings were 12-mm spot size, 6.0 to 6.5 J/cm^2, and 0.45 milliseconds. The mean age at the time of first treatment was 3.38 months (range, 5-355 days) and the mean number of treatments was 9.8 (range, 2-23; median, 10). Recommended treatment interval was every 2 to 3 weeks, with longer intervals for patients with darker skin. The mean treatment interval was 37.29 days (1.24 months). Patients who demonstrated complete clearance (mean VAS grade, 5) presented with

Table 1. Demographic Characteristics of 197 Patients

Characteristic	No. (%)
Sex	
Male	73 (37.1)
Female	124 (62.9)
Age	
Mean, mo	3.38
Range, d	5-355
Fitzpatrick skin types[a]	
I-III	179 (90.9)
IV	16 (8.1)
V-VI	2 (1.0)
Lesion location	
Face	149 (75.6)
Trunk/extremities	50 (25.4)
Periocular	81 (41.1)
Lesion size, cm^2	
Mean	61.09
Range	0.49-600
No. of treatments	
Mean	9.8
Range	2-23

[a] Fitzpatrick skin types: types I to III, light; type IV, medium brown; types V and VI, dark.

both a smaller average mean lesion size of 49.05 cm^2 and required fewer (8.1) treatments on average.

Per the mean physician VAS grading of 197 patients, 51 patients (25.9%) showed 100% clearance (mean [range] VAS score of 4.78 [4.5 - 5]); 81 patients (41.1%) showed 76 to 99% improvement (mean [range] VAS score of 3.91 [3.5 to <4.5]); 44 patients (22.3%) showed 51% to 75% improvement (mean [range] VAS score of 2.86 [2.5 to <3.5]); 13 patients (6.6%) showed 26% to 50% improvement (mean [range] VAS score of 2.12 [1.5 to <2.5]); and 8 patients (4.1%) showed 0 to 25% improvement (mean [range] VAS score of 0.78 [0 to <1.5]). The mean (SD) VAS grade for all patients was 3.65 (1.26) (median, 4), corresponding to excellent clearance (**Figure 1**). The mean VAS grade for facial lesions only was 3.69 (median score, 4) and for nonfacial locations (trunk and/or extremities), 3.57 (median score, 4). The mean VAS grade for ocular lesions was 3.62 (median score, 4).

Of the 149 patients with facial lesions, 19.8% had a V1 (first branch of the trigeminal nerve [ophthalmic nerve]) distribution; 32.0%, a V2 (second branch of the trigeminal nerve [maxillary nerve]) distribution; 4.6%, a V3 (third branch of the trigeminal nerve [mandibular nerve]) distribution; 12.2%, a V1/V2 distribution; 3.6%, a V2/V3 distribution; and 3.6%, a V1/V2/V3 distribution (**Table 2**). The mean VAS grades for each group were as follows: 3.98 (V1), 3.70 (V2), 3.17 (V3), 3.77 (V1/V2), 2.14 (V2/V3), and 3.93 (V1/V2/V3). The clearance scores were analyzed in quartiles corresponding to age at initiation of treatment (0-3, >3 to 6, >6 to 9, and >9 to 12 months). There was no statistically significant difference across the different age groups ($P > .05$). Three cases (2 on the legs of patients with skin types III and IV and 1 on the cheek of a patient with skin type IV) resulted in transient, mild hyperpigmentation that resolved within 2 years. The treatments did not result in scarring, hypopigmentation, or any other notable complications.

The presence of a V1 lesion was associated with a statistically significantly higher clearance rate by a VAS grade of 0.55 (95% CI, 0.25-0.84; $P < .001$) (**Table 3**). After controlling for lesion size and patient age, the presence of a V1 lesion was still associated with a statistically significantly higher clearance rate by a VAS grade of 0.51 (95% CI, 0.20-0.80; $P < .001$) and 0.54 (95% CI, 0.25-0.84, $P < .001$), respectively. The presence of a V3 lesion was a predictor associated with a statistically significant lower clearance rate by a VAS grade of 0.47 (95% CI, −0.91 to −0.02; $P = .04$) (Table 3). However, a V3 lesion effect appears to be explained, in part, by lesion size. When controlling for lesion size, the presence of a V3 lesion was no longer indicative of lower clearance rates to a statistically significant degree (95% CI, −0.01 to −0.89; $P = .05$).

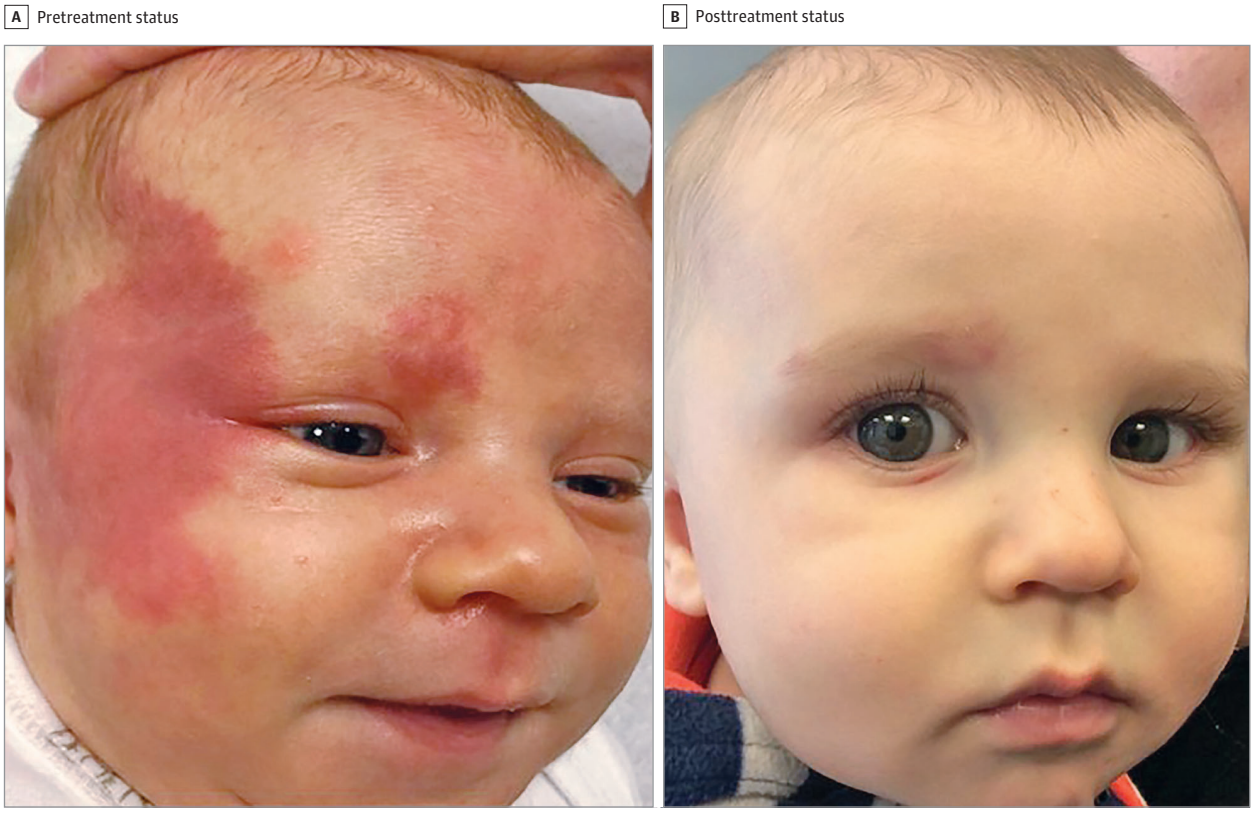
Discussion

Our study results suggest that treating PWSs early in life is most likely safe, with positive outcomes. All 197 patients received treatment at the age of 1 year or younger—as early as 5 days—and had an excellent clinical outcome (**Figure 2**). Both the facial and nonfacial lesions achieved a mean VAS grading of 3.65 (a score of 4 corresponds to a 76%-99% clearance and a score of 3 corresponds to a 51%-75% clearance) without any significant complication. Eighty-one patients (41.1%) with periocular involvement had excellent clearance without any adverse effects or complications. Two-thirds (66.5%) of the patients had 76% to 100% clearance. Given the small study population who received the first treatment between the ages of 6 and 12 months, further studies are needed to elucidate whether earlier intervention (eg, 0-3 vs 9-12 months) is associated with better results. Although our study results cannot be directly compared with prior studies owing to the lack of statistical power and difference in designs, the present study results also reflect better success rates for V1 compared with those of other dermatomes.

Dermatomal differences in response have been reported in the literature. Although newer studies suggest that facial PWS distribution follows embryonic vasculature of the face rather than the trigeminal nerve distribution,[10] data on dermatomal differences are helpful to understand anatomic differences in treatment response, especially in the context of prior studies. A retrospective study of 259 adults and children with PWSs[11] showed that V2 distribution resulted in only good response (mean lightening, 73.8%), whereas V1 and V3 distributions each showed excellent response (mean lightening, 83.6% and 82.5%, respectively). In another retrospective study of 49 infants who received their first PDL treatment at age 6 months or younger, the dermatomal clearance was as follows: V1 (93.8%), V2 (91.1%), V3 (84.3%), V1/V2 (83.7%), and V1/V2/V3 (81.0%).

The range of treatment settings used in the study reflects the real-world practice in which treatment settings are adjusted at each visit to maximize response. The typical initial

Figure 1. Treatment of a Port-Wine Stain



A comparison of the pretreatment photograph (A) at age 29 days and the posttreatment photograph after 8 sessions of pulsed dye laser treatment (B) shows excellent clearance at age 26 weeks.

Table 2. Dermatomal Distribution Data of Port-Wine Stains

Distribution[a]	Patients, No. (%)	VAS Grade, Mean
V1	39 (19.8)	3.98
V2	63 (32.0)	3.70
V3	9 (4.6)	3.17
V1/V2	24 (12.2)	3.77
V1/V2/V3	7 (3.6)	3.93
V2/V3	7 (3.6)	2.14
>1 Dermatome	38 (19.3)	3.50

Abbreviation: VAS, visual analog scale.

[a] V1, first branch of the trigeminal nerve (ophthalmic nerve); V2, second branch of the trigeminal nerve (maxillary nerve), and V3, third branch of the trigeminal nerve (mandibular nerve).

Table 3. Significance Level by Dermatomal Distribution

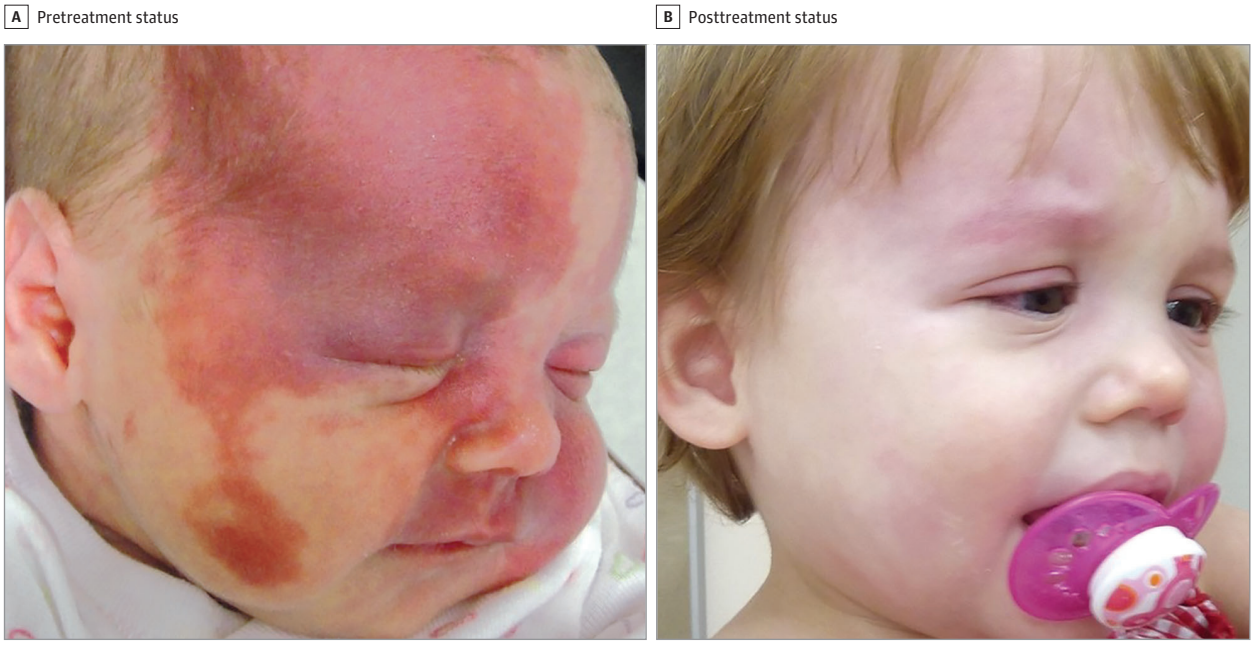
Area Affected[a]	95% CI	*P* Value
V1	0.25 to 0.84	<.001
V2	−0.38 to 0.20	.55
V3	−0.91 to −0.02	.04
>1 Dermatome	−0.43 to 0.31	.75

[a] V1, first branch of the trigeminal nerve (ophthalmic nerve); V2, second branch of the trigeminal nerve (maxillary nerve), and V3, third branch of the trigeminal nerve (mandibular nerve).

settings used for the face and neck lesions were 10-mm spot size, 8 to 9 J/cm^2, and 1.5 milliseconds. For the body lesions, the typical initial settings were 12-mm spot size, 6 to 6.5 J/cm^2, and 0.45 milliseconds. Within this narrow range, the laser measures were chosen and modified at each visit. The treatment variables were selected based on various factors, such as skin types, degree of responsiveness, and tolerability. In general, the clinical end goal of PDL treatment for PWSs was purpura.

Treating PWS early affords many advantages with regard to the treatment. Port-wine stains progress from being mostly patches to thicker plaques with time.[12] A retrospective review of 415 patients showed that approximately two-thirds of all patients with PWSs develop nodularity or hypertrophy in the fifth decade of life, with the mean age of hypertrophy being 37 years.[6] With time, the risk of spontaneous bleeding secondary to injury to the affected areas also increases. Significant hypertrophy of the PWS involving the periorbital or perioral region can affect the visual field, breathing, or eating. The treatment done in infancy is on lesions that have not yet grown in size and thickness, which minimizes both the duration and frequency of the laser treatment sessions. Furthermore, an infant's reduced skin thickness allows for better penetration of the laser beam. Skin thickness inversely correlates with laser treatment outcomes, and less collagen in the thinner skin allows for less back-scattering of laser,[13] which likely leads to a more effective laser treatment. Pathologic changes involved

Figure 2. Treatment of a Port-Wine Stain



A comparison of the pretreatment photograph (A) at the age of 10 days and the posttreatment photograph after 9 sessions of pulsed dye laser treatment (B) shows excellent clearance at age 5 months.

in PWSs, including an increase in the number of pericyte layers and basement membranes, are known to occur early in infancy,[14] and the timing of the laser treatment could play an important role in minimizing the growth of these lesions.

Despite these benefits to early clearance of PWSs, the timing of the initiation of laser treatment has been debated among clinicians. Laser treatment of PWSs in infants 6 months or younger has been demonstrated to be safe and effective,[15,16] and many clinicians support early intervention for these birthmarks.[17] However, there have been others who believe that treating at an earlier age is not more effective than treating at a later age, but such an opinion may be based on experience with older laser technology. For example, a 1998 report by van der Horst and colleagues[18] concluded that treating early did not make a difference based on their patients, who were treated using a flashlamp-pumped PDL with a spot size of 5 mm. The use of the older technology and small spot size likely resulted in slower treatment progress, and one could argue that earlier intervention was not attempted as often and was not as successful as the treatment possible with today's technology. Pain was also a major deterrent before the advent of dynamic cooling device technology, which was developed to minimize pain and for epidermal protection. Significant pain with treatments likely prevented clinicians from treating at the sufficient frequency required to achieve optimal clearance while maintaining safety.

In addition to the aforementioned medical benefits, there are psychological benefits of early treatment. Psychological morbidity resulting from PWSs has been well documented in the literature.[19,20] Patients with PWSs have been reported to have significantly higher emotional stress and impaired quality of life.[21] In addition to creating stressors for patients, PWSs also create stressors for the parents and can have negative family satisfaction effects.[22] A study of 259 patients with PWSs and their families reported significant relief of various psychological stressors, including low self-esteem, after laser treatment, and the authors called for early intervention of these disfiguring birthmarks.[23]

Although most patients in the study had lighter skin types (Fitzpatrick skin types I-III), all of the 18 children with darker skin types also did well, without any significant complications. Patients with darker skin types are also known to benefit from early and frequent treatment.[24] In a recent study of 39 East Asian patients ranging from age 3 months to 38 years,[25] short treatment intervals of 3 weeks with PDL have been reported to be safe and effective. Shi and colleagues[26] reported in their review of 848 Chinese patients with PWSs that the response rate to PDL was the highest (93.9%) in patients 1 year or younger when compared with older patients.

Initiating treatment during infancy avoids the need for general anesthesia as much as possible and can maximize the likelihood of clearance with frequent but safe treatment sessions.[27] With the growth of the child, it becomes more challenging to keep the patient stabilized for the duration of the treatment. Treating infants without anesthesia has its pros and cons. While the PDL treatment is not without pain—a single pulse of a PDL has been likened to the sensation of a rubber band snap[28]—the benefits of early treatment likely outweigh the potential risks.[29] Effort has been made to reduce the pain associated with the treatment, and using a cooling device, such as a dynamic cooling device, which sprays cryogen prior to the laser pulse, has been shown to significantly diminish pain during PWS

treatment.[30] Given that frequent treatments are often necessary to achieve acceptable clearance, being able to treat children without having to frequently expose them to general anesthetic and sedation drugs offers a safety advantage and cost savings. Laser treatments should be performed by experienced physicians, and appropriate eye protection must be used. For PWSs involving the periocular region, metal eye shields can be safely placed after applying an ophthalmic anesthetic solution while the nursing staff helps to stabilize the patient's head. In the hands of experienced physicians, corneal shields can be placed quickly and are well tolerated by the patients (**Video**). Every effort should be made to minimize the duration of restraint with the help of experienced staff members.

Limitations

The present study results are limited by the retrospective design, which has inherent limitations of variable follow-up and a lack of control group. The assessments were performed on photographs that were not standardized, although patients whose photographs did not show the PWS clearly were excluded from the study. However, the effectiveness of the treatments may be higher than the image presented given that the follow-up photographs were pretreatment photographs of their last visit. Most patients who do well and do not require further treatments do not return for additional visits, which may have led us to capture more of those patients who needed additional treatments. It is also likely that additional treatments beyond the first year may lead to further clearance. Given that our retrospective data were limited to a finite period, we do not have long-term data on recurrence. It may be helpful to examine the topic in a prospective study, which could help to better quantify the incidence, extent, and timing of any recurrence.

Conclusions

In this study, treatment of PWS in infancy was both safe and effective. In our study, we were able to achieve 100% clearance of the vascular birthmark in 34.0% of patients younger than 1 year. We also found that the presence of a V1 lesion was associated with a statistically significant higher clearance rate. We believe the rationale and the data that we present herein support early in-office treatment, particularly when the treatment can be performed with minimal risk for complications. Additional studies, particularly evaluating long-term outcomes, on the safety and effectiveness of treating PWSs during infancy would be beneficial and further guide clinicians.

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Concept and design: Jeon, Geronemus.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Jeon, Ghalili, Geronemus.
Critical revision of the manuscript for important intellectual content: All authors.
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Administrative, technical, or material support: Jeon, Geronemus.
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