

EFFECT OF THE TIMING OF TREATMENT OF PORT-WINE STAINS WITH THE FLASH-LAMP-PUMPED PULSED-DYE LASER

CHANTAL M.A.M. VAN DER HORST, M.D., PETRA H.L. KOSTER, M.D., CORIANNE A.J.M. DE BORGIE, M.D., PATRICK M.M. BOSSUYT, PH.D., AND MARTIN J.C. VAN GEMERT, PH.D.

ABSTRACT

Background Port-wine stains can be treated with a flash-lamp-pumped pulsed-dye laser, but it is uncertain whether this treatment is more effective if administered early in life, when the skin is thinner and the lesion is smaller.

Methods We prospectively studied 100 patients with a previously untreated port-wine stain of the head or neck. They were treated with the flash-lamp-pumped pulsed-dye laser and divided into four age groups (0 to 5, 6 to 11, 12 to 17, and 18 to 31 years). The outcome measure was lightening of the port-wine stain (reduction in the difference in color between the skin with the stain and contralateral healthy skin) as measured with a colorimeter after an average of five treatments (range, three to seven) of the entire lesion.

Results Of the 100 patients, 11 could not be included in the analysis because they had received fewer than three or more than seven treatments, had an erroneous base-line color measurement, or were lost to follow-up. The sizes, locations, and colors of the port-wine stains were similar among the groups. When all 89 patients were analyzed together, the average reduction in the difference in color between the skin with the port-wine stain and contralateral healthy skin was 40 percent. The differences between age groups in the average reduction in color differences were not significant ($P=0.26$). By the end of the study, only 7 of 89 patients had completed laser therapy, and in no case was clearance complete. Treatment was discontinued in all seven because the last three treatments did not lead to further lightening.

Conclusions We found no evidence that treatment of port-wine stains with the flash-lamp-pumped pulsed-dye laser in early childhood is more effective than treatment at a later age. (N Engl J Med 1998; 338:1028-33.)

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PORT-WINE stains are congenital vascular malformations that occur in an estimated 3 children per 1000 births.¹ The stigma of a disfiguring facial birthmark may have a substantial effect on a child's social and psychosocial adjustment.²⁻⁵ Many methods have been used to reduce the visibility of port-wine stains — ionizing radiation, cryotherapy, tattooing, and surgery — but all with unfavorable results. In the 1980s argon-laser therapy became the treatment of choice for adult patients. In children, however, serious scarring was reported with this technique, making it a less attrac-

tive alternative.^{6,7} In 1985 the flash-lamp-pumped pulsed-dye laser was introduced. This laser was especially advocated for the treatment of port-wine stains in children because of its high specificity and safety. The wavelength of the laser and the duration of the pulse are chosen to produce thermal injury that remains confined to the targeted port-wine-stain vasculature (selective photothermolysis).⁸ Consequently, the scarring of skin seen with other lasers should not occur. Treatment with a flash-lamp-pumped pulsed-dye laser was hypothesized to be more effective in children than adults because the skin in children is thinner and the size of the port-wine stain is smaller: fewer treatments would therefore be necessary to achieve optimal clearance.^{3,4,9-12} These are all arguments to initiate treatment at an early age.

Better results with early treatment were reported by Tan et al.³ but were not unequivocally confirmed by others.¹³⁻¹⁶ However, these studies were all retrospective, and none used objective measurements to assess the results.

In a prospective study we investigated whether treatment of a port-wine stain at a young age would yield better results than treatment at an older age. We assessed the degree of lightening of the port-wine stain by measuring the reduction in the difference in color between the skin with the port-wine stain and the contralateral healthy skin with a colorimeter.¹⁷

METHODS

One hundred patients with a previously untreated port-wine stain of the head or neck were treated with the flash-lamp-pumped pulsed-dye laser. The study protocol was reviewed and approved by the local hospital review committee. Patients 31 years of age or younger who had had no prior treatment of their port-wine stain were eligible. Consecutive patients who met the entry criteria were seen at the Academic Medical Center in Amsterdam between December 1991 and March 1995. Oral informed consent was obtained from the patients or their parents or guardians. Almost all patients referred themselves after learning about the laser treatment through the media.

During the first consultation, the extent and location of the port-wine stain were recorded as well as the presence of hypertrophy and neurologic and ophthalmologic symptoms. Patients were divided into four age groups of 25 patients each: 0 to 5 years, 6 to

From the Department of Plastic Reconstructive and Hand Surgery (C.M.A.M.H., P.H.L.K.), the Department of Clinical Epidemiology and Biostatistics (C.A.J.M.B., P.M.M.B.), and the Laser Center (M.J.C.G.), Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands. Address reprint requests to Dr. van der Horst at the Department of Plastic Reconstructive and Hand Surgery, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands.

11 years, 12 to 17 years, and 18 to 31 years. Enrollment in an age group ended as soon as 25 consecutive patients had entered the group. All patients were treated with a Candela flash-lamp-pumped pulsed-dye laser (model SPTL-1) with a wavelength of 585 nm, a pulse duration of 0.45 msec, a spot size of 5 mm, and a level of radiant exposure of 6 to 8 J per square centimeter. The pulses overlapped slightly. Each port-wine stain was cooled during treatment with gauze dressings drenched with ice water. After treatment, no antibiotic creams were used. Treatment of the same area was repeated at intervals of at least eight weeks.

Laser therapy was provided in an outpatient setting. Most port-wine stains could be treated only partially at each visit, especially in children. Several visits were necessary to treat the entire port-wine stain once. A series of treatments of the entire port-wine stain was required to achieve optimal clearance. If necessary, pain was reduced with a eutectic mixture of lidocaine and prilocaine (Emla; a mixture whose melting point is lower than the melting

points of either lidocaine or prilocaine), nerve block, or both. The need for repeated visits caused increasing anxiety in the children, which sometimes forced us to add midazolam for sedation. If this was insufficient, subsequent therapy was performed with the patient under general anesthesia.

Before the first treatment, slides were taken by a professional photographer in a studio under standardized conditions of illumination and with the same type of camera, diaphragm, enlargement, film, and processing technique for each patient. Color-control patches (Eastman Kodak) were photographed at the end of each series of slides. Photographs were taken in full view, profile, and $\frac{3}{4}$ position. Copies of all slides were kept in the photographic department, a procedure that allowed patients to be positioned in the same way during each photographic session.

Color was measured with a Minolta chromometer (model CR-300).¹⁷ This hand-held, microprocessor-controlled, operator-independent reflectance photometer with a digital readout uses a

TABLE 1. BASE-LINE CHARACTERISTICS OF THE 89 PATIENTS.*

CHARACTERISTIC	0-5 YR OF AGE (N=21)	6-11 YR OF AGE (N=24)	12-17 YR OF AGE (N=21)	18-31 YR OF AGE (N=23)
Sex — M/F	7/14	10/14	6/15	8/15
Age — yr	2.1±1.9	7.6±1.6	14.9±1.7	22.7±3.3
Port-wine stain				
Absolute surface area — cm ²	71±63	123±147	99±79	139±172
Location — no. of patients				
Left side	4	11	9	15
Right side	15	9	11	5
Left and right sides	2	4	1	3
Hypertrophy — no. of patients (%)	4 (19)	9 (38)	4 (19)	4 (17)
Ophthalmologic disorders — no. of patients (%)†	2 (10)	3 (12)	0	3 (13)
Neurologic disorders — no. of patients (%)‡	0	2 (8)	0	2 (9)

*Plus-minus values are means ±SD.

†The disorders consisted of elevated eye pressure and glaucoma.

‡The disorders consisted of epileptic insults and hemiplegia.

TABLE 2. TREATMENT CHARACTERISTICS AND THE AVERAGE DIFFERENCE IN COLOR BEFORE AND AFTER AN AVERAGE OF FIVE TREATMENTS OF THE ENTIRE PORT-WINE STAIN IN THE FOUR AGE GROUPS.*

CHARACTERISTIC	0-5 YR OF AGE (N=21)	6-11 YR OF AGE (N=24)	12-17 YR OF AGE (N=21)	18-31 YR OF AGE (N=23)	P VALUE
Average number of visits per patient†	10±4	11±5	10±6	9±5	—
Level of radiant exposure (J/cm ²)	6.5±0.4	6.7±0.4	6.9±0.4	6.9±0.5	—
Number of pulses per visit†	200±276	217±333	223±156	227±175	—
General anesthesia (no. of patients)	11	5	0	0	—
Headaches after treatment (no. of patients)	4	4	3	7	—
Completed treatment (no. of patients)	0	1	2	4	—
With adequate clearance	0	0	1	3	—
Difference in color between port-wine stain and contralateral healthy skin					
Before treatment‡	14.5±4.2	16.7±4.6	16.1±5.5	14.6±5.9	0.39
After treatment‡	9.5±4.3	9.5±4.2	8.6±4.2	9.0±4.3	0.86
Improvement‡	5.0±4.1	7.2±3.5	7.6±5.4	5.7±4.4	0.19
Relative improvement (%)	33±26	43±17	45±20	37±23	0.26

*Plus-minus values are means ±SD.

†During each visit the largest possible area of the port-wine stain was treated; several visits were required to treat the entire port-wine stain.

‡The values were obtained with the L*a*b* system as described in the Methods section.



Figure 1. Examples of Clinical Results.

The reported degree of lightening is measured with a colorimeter. Panel A shows a three-year-old child before treatment (left-hand side) and 2½ years later, after six treatments (right-hand side). The degree of lightening is 48 percent. Panel B shows a 17-year-old patient before treatment (left-hand side) and 1½ years later, after six treatments (right-hand side). The degree of lightening is 84 percent.

measuring area 8 mm in diameter and diffuse daylight illumination (standard illuminant, D65). The perceived color of the skin is fully quantified on the basis of the proportions of red, green, and blue present in the spectral skin reflectance. The approach of this method is equivalent to the way in which the human eye perceives light. The chromometer uses the $L^*a^*b^*$ system, devised in 1976 by the Commission Internationale de l'Éclairage to ensure that equal distances on a chromaticity diagram correspond to equal perceived differences in color. In this system, L^* denotes lightness, representing the object's reflectance relative to a 100 percent ideal reflecting diffuser (on a scale of 0 to 100, in which 0 represents black and 100 white); a^* denotes values from green to red (negative values indicate green, and positive values red); and b^* denotes values from blue to yellow (negative values indicate blue, and positive values yellow).¹⁸ The difference in the color between the skin with the port-wine stain and contralateral healthy skin was calculated from the standard equation $\sqrt{(\Delta L^*)^2 + (\Delta a^*)^2 + (\Delta b^*)^2}$, where ΔL^* , Δa^* , and Δb^* represent the differences in the respective measured $L^*a^*b^*$ values. Color variables (i.e., L^* , a^* , b^* , and their differences) have no physical unit, because reflection coefficients as well as their primary color

contents are dimensionless. As an example, the $L^*a^*b^*$ values for the dark-red port-wine stain shown on the left-hand side of Figure 1A are 48.4 for L^* , 32.8 for a^* , and 11.8 for b^* . For the contralateral healthy skin, the respective values are 56.4, 18.6, and 13.3. Therefore ΔL^* equals 8, indicating that the port-wine stain is darker than the healthy skin; Δa^* equals 14.2, indicating that the stain is much redder than the healthy skin; and Δb^* equals 1.5, indicating that the skin with the lesion is slightly less yellow than the healthy skin. The difference in color is thus 16.4, which is large relative to just-perceivable differences in color, with values of about 0.5 to 1.

We analyzed the reproducibility of the color measurements by measuring the same location twice in a single session in each patient before treatment and calculating the intraclass correlation coefficient¹⁹ (the contribution of the true variance to the total variance of measurements). This coefficient was 0.98 for the total patient population (95 percent confidence interval, 0.98 to 1.0), implying that the reproducibility of results was good. Most of the color measurements were performed by the same treating physician, but some were made by two other therapists. The digital readouts of color measurements were stored in a computer in



B

combination with the locations of the measurements. For each patient subsequent color measurements were made at the same location.

After an average of five treatments (range, three to seven) of the entire port-wine stain, color measurements and standardized photography were repeated at least eight weeks after the last visit. Treatment was discontinued if either the port-wine stain had disappeared or the three previous consecutive treatments had not resulted in any further lightening.

The outcome measure in each age group was the average reduction in the difference in color between the skin with the port-wine stain and the contralateral healthy skin after an average of five treatments of the entire lesion. We used one-way statistical analysis of variance to compare the distribution of and reduction in color differences between the four age groups.¹⁹ All calculations of P values were two-tailed.

RESULTS

Eleven of the 100 patients could not be included in the analysis. Three patients (12 to 17 years of age) received fewer than three treatments, and none had complete clearance of the port-wine stain. One patient (in the group of patients who were 12 to 17 years of age) was lost to follow-up after four treatments without complete clearance and without a fi-

nal color measurement having been obtained. One patient in the oldest age group had her pretreatment color measurement when there was a technical problem with the equipment. The problem was discovered after laser treatment had been started, so the measurement could not be repeated. The other six patients received more than seven treatments; they had had no color measurements between treatments 3 and 7, but none had complete clearance of the port-wine stain. Four of the six were in the group that was 0 to 5 years of age (8, 8, 9, and 9 treatments), one was in the group that was 6 to 11 years of age (10 treatments), and one was in the group that was 18 to 31 years of age (8 treatments).

The base-line characteristics of the 89 patients included in the analysis are shown in Table 1. There were more females than males in every age group. The mean size of the lesion was largest in the oldest age group, although there was no significant difference in the size of the lesion between the groups ($P=0.39$ by the Kruskal-Wallis test). The locations of the port-wine stains were similar among the four

groups. The cheek was the area most often involved. The pretreatment color measurements were similar among groups.

Treatment characteristics, complications, and results are given in Table 2. Examples of the clinical results are shown in Figure 1. General anesthesia had to be used in 16 of the 45 children in the youngest age groups. In the absence of general anesthesia in these two groups, fewer pulses could be given per visit. With the use of anesthesia, the mean number of pulses per visit was similar in the four groups. There were few local complications. The blue discoloration of the skin that occurred during the first 7 to 10 days after treatment was perceived as annoying. Small blisters or crusting was reported, but in no case resulted in scarring or infection. Eighteen patients reported headaches after treatment that in some cases mimicked migraine headaches. No patient required hospitalization because of complications.

At the time of evaluation, only 7 of the 89 patients had completed laser therapy. In no patient did the difference in color between the skin with the lesion and the contralateral healthy skin reach a value of zero. All seven discontinued therapy because no further clearance of the port-wine stain had been achieved in the last three treatments. Four of these seven patients perceived the level of clearance as adequate: one (in the group 12 to 17 years of age) after four treatments, one after three treatments, one after five treatments, and one after seven treatments (all three in the group 18 to 31 years of age). Three of the seven patients had incomplete clearing of the port-wine stain: one (in the group 6 to 11 years of age) after seven treatments, one (in the group 12 to 17 years of age) after five treatments, and one (in the group 18 to 31 years of age) after six treatments.

Analysis of variance showed that the differences among age groups in the average reduction in the difference in color between the skin with the port-wine stain and the contralateral healthy skin were not significant ($P=0.26$). When all patients were analyzed together, the average reduction in the difference in color was 40 percent.

DISCUSSION

We did not confirm the hypothesis that treatment of port-wine stains at an early age is more effective than treatment at a later age. After an average of five treatments (range, three to seven) of the entire port-wine stain in 89 patients, the difference in color between the skin with the port-wine stain and the contralateral healthy skin was reduced by 40 percent on average, regardless of age. Some port-wine stains require far more than 7 treatments, in some cases as many as 25, to achieve the best possible clearance.²⁰ It is therefore likely that with further therapy a higher average rate of clearance would have been achieved.

The rates of clearance, which were based on ob-

jective measurements, were relatively low as compared with some previously published data. However, the earlier studies were all retrospective and used subjective methods of evaluation.^{3,10-16} Furthermore, recent data suggest that a small port-wine stain or a superficial location of vessels with large diameters correlates with a good response to treatment with the flash-lamp-pumped pulsed-dye laser.^{21,22} Often, the size of the lesion was either not reported^{3,9-11} or smaller than in our series,^{16,20} or more treatments were given at the time of evaluation.^{16,20}

Tan et al.³ treated 35 children and reported a fast response and high clearance rates, especially in those under seven years of age. However, they used a wavelength of 577 nm and included only patients with light (pink-red) stains, a combination that is generally found to have the best response to treatment with the flash-lamp-pumped pulsed-dye laser.^{23,24} We used a laser wavelength of 585 nm, and the numbers of patients with light and with dark stains were equally distributed among the four age groups. Reyes and Geronemus⁹ reported fast rates of clearance of port-wine stains among children, but their laser values were not specified (a wavelength of either 577 or 585 nm and a pulse duration of either 0.36 or 0.45 msec). Alster and Wilson,¹⁶ without specifying the initial color of the lesion and with lesions of smaller average size than in our study, reported that the number of treatments necessary to clear port-wine stains in children 9 to 16 years of age and patients over 16 years of age was not greater than the number required to treat port-wine stains in infants (0 to 2 years of age) and children who were less than 9 years of age. Ashinoff and Geronemus,¹² studying a group of only 12 infants under seven months of age who mainly had pale-pink port-wine stains, reported that results were optimal when treatment was begun before the age of seven months. We cannot compare our data with theirs, because only five children in our study were younger than seven months at the beginning of treatment. These children did not finish treatment early.

General anesthesia was necessary in 36 percent of the children who were under 12 years of age. Although some investigators reported they did not use general anesthesia,^{3,4,16} our experience has been confirmed by others.^{11,25}

Only 7 of 89 patients completed treatment during the study. This confirms^{16,20,22} that the number of treatments required for maximal clearance of port-wine stains is more than previously reported.³

Our results have implications for the timing of therapy in children. Although facial port-wine stains can be treated effectively and safely early in life, treatment at a later age leads to similar results. Therefore, the age at which therapy is initiated should be based on a careful weighing of the anticipated benefit²⁶ and the discomfort of treatment.

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