Chapter 3

Effect of the timing of treatment of port-wine stains with the flash-lamp-pumped pulsed-dye laser.

Chantai 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.

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.


Supported by a grant (OG 92/004) from the Dutch Health Insurance Council.
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 and neck. They were treated with the flash-lamp-pumped pulsed dye-laser and divided in 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.
Introduction

Port-wine stains are congenital vascular malformations that occur in an estimated 3 children per 1000 births. The stigma of a disfiguring facial birthmark may have a substantial effect on a child’s social and psychosocial adjustment. 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 attractive alternative. 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). Consequently, the scarring of skin seen with other lasers does 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. These are all arguments to initiate treatment at an early age.

Better results with early treatment were reported by Tan et al. but were not unequivocally confirmed by others. 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.

Methods

One hundred patients with a previously untreated port-wine stain of the head and 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 no prior treatment of their port-wine stain were eligible. Consecutive patients who met the entry criteria were seen in 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, neurologic and ophthalmologic symptoms. Patients were divided into four age groups, consisting of 25 patients each: 0 to 5 years, 6 to 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 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 children, which sometimes forced us to add midazolam or 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 photostudio 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 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). This hand-held, microprocessor-controlled, operator-independent reflectance photometer with a digital readout uses a 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’Eclairage” 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). The difference in 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 $\Delta L*$, $\Delta a*$ and $\Delta b*$ represent the difference 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 $\Delta L*$ equals 8, indicating that the port-wine stain is darker than the healthy skin; $\Delta a*$ equals 14.2, indicating that the stain is much redder than the healthy skin; and $\Delta b*$ 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 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 coefficient\(^1\) (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: 0.98-1.0), 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 combination with the localizations 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 final 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 had received more than seven treatments; they had had no color measurement 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 in group that was 6 to 11 years of age (10 treatments), and one in 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 Kruskall-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 out 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). 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 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 objectively 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
reported³,⁶-¹¹ 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 therapy.²¹,²⁴ We used a laser wavelength of 585 nm, and the number of
patients with light and with dark stains were equally distributed among the four age
groups. Reyes and Geronemus\textsuperscript{9} reported fast rates of clearance of port-wine stains among children, but their laser values were not specified (a wave length of either 577 nm and a pulse duration of either 0.36 or 0.45 msec.) Alster and Wilson,\textsuperscript{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,\textsuperscript{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,\textsuperscript{3,4,16} our experience has been confirmed by others.\textsuperscript{11,25} Only 7 of the 89 patients completed treatment during the study. This confirms\textsuperscript{16,20,22} that the number of treatments required for maximal clearance of port-wine stains is more than previously reported.\textsuperscript{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 benefit,\textsuperscript{26} and the discomfort of treatment.
Addendum

Fig. 1. Examples of Clinical Results.

The reported degree of lightening is measured with a colorimeter. Panel A (page 30) 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 (page 31) shows a 17-year-old patient before treatment (left-hand side) and ½ years later, after six treatments (right-hand side). The degree of lightening is 84 percent.
### Table 1. Base-Line Characteristics of the 89 Patients.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>0-5 Yr of Age (N=21)</th>
<th>6-11 Yr of Age (N=24)</th>
<th>12-17 Yr of Age (N=21)</th>
<th>18-31 Yr of Age (N=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex - M/F</strong></td>
<td>7/14</td>
<td>10/14</td>
<td>6/15</td>
<td>8/15</td>
</tr>
<tr>
<td><strong>Age - yr</strong></td>
<td>2.1±1.9</td>
<td>7.6±1.6</td>
<td>14.9±1.7</td>
<td>22.7±3.3</td>
</tr>
<tr>
<td><strong>Port-wine stain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute surface area - cm²</td>
<td>71±63</td>
<td>123±147</td>
<td>99±79</td>
<td>139±172</td>
</tr>
<tr>
<td>Location - no. of patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left side</td>
<td>4</td>
<td>11</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>Right side</td>
<td>15</td>
<td>9</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Left and right sides</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td><strong>Hypertrophy - no. of patients (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 (19)</td>
<td>9 (38)</td>
<td>4 (19)</td>
<td>4 (17)</td>
</tr>
<tr>
<td><strong>Ophthalmologic disorders - no. of patients (%)</strong></td>
<td>2 (10)</td>
<td>3 (12)</td>
<td>0</td>
<td>3 (13)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Neurologic disorders - no. of patients (%)</strong>†</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

*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.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>0-5 Yr of Age (N=21)</th>
<th>6-11 Yr of Age (N=24)</th>
<th>12-17 Yr of Age (N=21)</th>
<th>18-31 Yr of Age (N=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average number of visits per patient†</td>
<td>10±4</td>
<td>11±5</td>
<td>10±6</td>
<td>9±5</td>
</tr>
<tr>
<td>Level of radiant exposure (J/cm²)</td>
<td>6.5±0.4</td>
<td>6.7±0.4</td>
<td>6.9±0.4</td>
<td>6.9±0.5</td>
</tr>
<tr>
<td>Number of pulses per visit†</td>
<td>200±276</td>
<td>217±33</td>
<td>223±156</td>
<td>227±175</td>
</tr>
<tr>
<td>General anesthesia (no. of patients)</td>
<td>11</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Headaches after treatment (no. of patients)</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Completed treatment (no. of patients)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>With adequate clearance</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Difference in color between port-wine stain and contralateral healthy skin</td>
<td>14.5±4.2</td>
<td>16.7±4.6</td>
<td>16.1±5.5</td>
<td>14.6±5.9</td>
</tr>
<tr>
<td>Before treatment‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After treatment‡</td>
<td>9.5±4.3</td>
<td>9.5±4.2</td>
<td>8.6±4.2</td>
<td>9.0±4.3</td>
</tr>
<tr>
<td>Improvement‡</td>
<td>5.0±4.1</td>
<td>7.2±3.5</td>
<td>7.6±5.4</td>
<td>5.7±4.4</td>
</tr>
<tr>
<td>Relative improvement (%)</td>
<td>33±26</td>
<td>43±17</td>
<td>45±20</td>
<td>37±23</td>
</tr>
</tbody>
</table>

*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.
References


To the editor.

Van der Horst et al. (April 9 issue) report no additional benefit from early treatment of port-wine stains with the pulsed-dye laser, which is in contradiction to our experience and that of others. Several issues should be raised about the methods of the study, which may account for the unexpected results.

The authors enrolled consecutive patients in their treatment groups without controlling for the types or locations of the lesions. There were more “hypertrophic” lesions in the younger treatment groups (29 percent) than in the older treatment groups (18 percent). Hypertrophy of port-wine stains in childhood has not been reported previously, suggesting that lesions with an arterial or venous component may have been treated. Such lesions are known to be poorly responsive to pulsed-dye laser treatment. Van der Horst et al. also failed to control for the location of lesions on the head and neck, which we have reported to affect the response to pulsed-dye laser treatment.

The use of ice cubes to cool lesions during treatment may have led to chilling of dermal vessels in younger patients, who have thinner skin, thereby interfering with the efficacy of laser treatment. By treating port-wine stains only partially at each visit and by requiring several sessions to treat the entire port-wine stain, van der Horst et al. provided few complete treatments early on, potentially missing a therapeutic window of opportunity, when the skin is thinner and the stain smaller.

The treatment technique and technology that were used are outdated. Improved therapeutic outcomes have been demonstrated with the use of larger spot sizes – 7 to 10 mm – rather than the 5-mm spot size used by van der Horst et al. Additional benefit has been derived from the use of longer wavelengths (595 nm, as compared with 585 nm) and longer pulse durations (1.5 msec, as compared with 0.45 msec), in particular for hypertrophic lesions. Selective epidermal cooling can be achieved with cryogen-spray cooling, which is now being utilized in conjunction with 585-nm and 595-nm pulsed-dye laser treatment, decreasing the pain of treatment and the time needed for recovery.

Arielle N.B. Kauvar, M.D.
Roy G. Geronemus, M.D
317 E, 34th St.
New York, NY 10016.

The authors reply:

To the editor.

At the start of our study it was clear from other series involving small numbers of patients that port-wine stains in children could be treated safely with the flash-lamp-pumped pulsed-dye laser. Our prospective study, using objective color measurements and validated instruments to measure disfigurement, tested the hypothesis that port-wine stains in children could be treated more effectively than those in adults.

We included patients with capillary malformations alone. We defined hypertrophic port-wine stains in this population as lesions that were abnormally swollen in comparison with the healthy skin on the contralateral side. Patients with combined malformations (venous, arteriovenous, and lymphatic) were excluded. In our opinion, patients with Sturge-Weber syndrome have capillary malformations, and there is no evidence that treatment of port-wine stains that are part of such a syndrome is less effective than treatment of port-wine stains that are not part of a syndrome.

Before beginning treatment, we recorded the extent and location of the port-wine stain in each patient. We made an anatomical diagram of the face and neck in 64 regions and then regrouped these regions into 18 principal regions. We evaluated the response to treatment of the port-wine stain in relation to these regions within the age groups. We did not observe differences in responses that were related to the anatomical locations of the port-wine stains. In determining the response to treatment, we found that the initial size and depth of the lesion were more important predictive factors than the location of the lesion.

We only used gauze drenched in ice water, not ice cubes, for a short period after the laser pulses. The question is whether the vascular response to this type of pain relief differs from the vasoconstriction induced by a eutectic mixture of lidocaine and prilocaine (Emla cream), which is not known to interfere with the efficacy of treatment. Therapy was standardized; therefore, we did not change the laser settings during the study period. The use of a faster laser with a larger spot size (7 mm) would not have influenced the use of general anesthesia in our youngest age groups. In children with port-wine stains that could be treated partially during one visit, the entire lesion was treated within six to eight weeks. We included only a few children under the age of one year, therefore, it is still unclear whether such patients will ultimately have better treatment results than those treated at an older age. The additional benefit of the use of longer wavelengths and pulse durations remains to be established. Nonetheless, our main conclusion – that treatment of port-wine stains in early childhood is effective, but not more so than treatment at a later age – is unlikely to change.

Chantal M.A.M. van der Horst, M.D.
Corianne A.J.M. de Borgie, M.Sc.
Patrick M.M. Bossuyt, Ph.D.
Academic Medical Center, Amsterdam.


