ORIGINAL ARTICLE

Redarkening of Port-Wine Stains 10 Years after Pulsed-Dye–Laser Treatment

Menno Huikeshoven, M.D., Ph.D., Petra H.L. Koster, M.D., Ph.D., Corianne A.J.M. de Borgie, M.D., Ph.D., Johan F. Beek, M.D., Ph.D., Martin J.C. van Gemert, Ph.D., and Chantal M.A.M. van der Horst, M.D., Ph.D.

ABSTRACT

BACKGROUND

Although pulsed-dye–laser therapy is currently the gold standard for the treatment of port-wine stains, few objective data are available on its long-term efficacy. Using objective color measurements, we performed a 10-year follow-up of a previously conducted prospective clinical study of the treatment of port-wine stains with a pulsed-dye laser.

METHODS

We invited the patients to undergo repeated color measurements performed by the same procedures as in the previous study. The results at long-term follow-up were compared with color measurements obtained before treatment and after completion of an average of five laser treatments of the complete port-wine stain. A questionnaire was used to investigate patients' satisfaction with the treatment and their perception of long-term changes in the stain.

RESULTS

Of the 89 patients from whom color measurements were obtained in the previous study, 51 were included in this study. The patients had received a median of seven additional treatment sessions since the last color measurement, which had been made after an average of five treatments. The median length of follow-up was 9.5 years. On average, the stain when measured at follow-up was significantly darker than it was when measured after the last of the initial five laser treatments ($P=0.001$), but it was still significantly lighter than it was when measured before treatment ($P<0.001$). Fifty-nine percent of patients were satisfied with the overall treatment result. Six percent of patients reported that the stain had become lighter since their last treatment, 59% that it was unchanged, and 35% that it had become darker.

CONCLUSIONS

Using objective color measurements, we observed significant redarkening of port-wine stains at long-term follow-up after pulsed-dye–laser therapy. Patients should be informed about the possibility of redarkening before beginning treatment.

From the Department of Plastic, Reconstructive, and Hand Surgery (M.H., P.H.L.K., C.M.A.M.H.), the Laser Center (M.H., J.F.B., M.J.C.G.), and the Department of Clinical Epidemiology and Biostatistics (C.A.J.M.B.), Academic Medical Center, University of Amsterdam, Amsterdam. Address reprint requests to Dr. Huikeshoven at the Department of Plastic, Reconstructive, and Hand Surgery, G4-226 Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands, or at m.huikeshoven@amc.uva.nl.

N Engl J Med 2007;356:1235-40.

Port-wine stains are capillary malformations seen in approximately 0.3% of newborns. In this benign skin disorder, ectatic dermal venules cause the characteristic red skin color. Since the report by Tan and colleagues in 1989,[1] treatment with the pulsed-dye laser has been the gold standard. Although there has been much research on the short-term efficacy of the treatment, long-term follow-up information is scarcely available and is limited to case reports[2] and questionnaires.[3-8] We present the long-term follow-up results of a previously published prospective study that used objective color measurements to investigate the effect of the timing of pulsed-dye–laser treatment of port-wine stains.[9]

METHODS

The investigators in the previous study performed color measurements on 89 of 100 evaluated patients with previously untreated port-wine stains on the face or neck. The measurements were performed before treatment and after an average of five pulsed-dye–laser treatments of the complete stain. (One treatment of the complete stain may consist of more than one session.) In the present study, 51 of these patients underwent repeated color measurements and completed an evaluation questionnaire. Patients who had received additional treatment for their stains outside the study hospital after the first five treatments were excluded from the present study, as were patients who could not be located or who declined to participate.

The stains were treated with a Candela pulsed-dye laser (model SPTL-1) with a wavelength of 585 nm, a radiant exposure level of 6 to 8 J per square centimeter per pulse, a pulse duration of 45 msec, and a spot size of 5 to 7 mm. The area of the stain was cooled during treatment with gauze dressings drenched in ice water. Color measurements were performed as described in detail in the previous study.[9] In short, the color of both the stain and the contralateral normal skin was measured with a Minolta chromometer (model CR-300) that used the L*a*b* color coordinate system, where L* denotes lightness, a* values from green to red, and b* values from blue to yellow. The difference in color between the stain and the normal skin was calculated using the L*a*b* coordinates and was denoted by ΔE. A small number for ΔE indicates a small color difference, and a large number for ΔE indicates a large difference. A review of the literature suggests that a ΔE value of 1 is the least noticeable difference by a human observer under optimal viewing conditions.[10]

In the previous study, the face and neck were mapped into 64 different areas, and the color of the skin at baseline was measured at the darkest spot in the darkest area of the port-wine stain.[9] The location of the measurement was accurately documented on transparent overlays placed over photographs of the stain, and the overlays were used to ensure that the color was measured at the same location before treatment, after five treatments of the entire stain, and at long-term follow-up. The color both of the stain and of the normal skin was measured twice at the same location, and the average values were used. For each patient, the values for ΔE at long-term follow-up were compared with those determined in the previous study.

Each patient was asked two questions to evaluate the perception of the outcome of the treatment: Were you satisfied with the result at the end of treatment (which included any treatment sessions subsequent to the measurement taken after the first five treatments)? Since the last treatment session, has the stain become lighter, become darker, or remained the same color?

Since the previous study found no correlation between the age of the patient at treatment and the effect of treatment, we did not perform age-dependent analysis in the present study. All data sets were tested for normal distribution. Not all were normally distributed, and therefore the results are presented as medians with interquartile ranges, unless specified otherwise. Differences between groups in baseline characteristics and differences in ΔE values between follow-up and previous measurements were analyzed by nonparametric tests.

The study was approved by the hospital institutional review board. Written informed consent was obtained from each patient or the patient's parent.

RESULTS

PATIENTS AND FOLLOW-UP

Table 1 shows the characteristics of the patients and the results of color measurements. Of the 89 patients included in the previous study, 13 could not be traced and 15 declined to participate or

Table 1. Patient Characteristics and Results of Color Measurements.*

Variable	All Patients (N=89)	Patients Included in Follow-up Study		Patients Excluded from Follow-up Study	
		Total (N=51)	Subgroup 1 (N=6)†	Total (N=38)	Subgroup 2 (N=10)‡
Female sex (%)	65	75	67	53	60
Age at follow-up (yr)					
Mean	24	23	30	25	24
Range	12 to 42	12 to 42	23 to 41	13 to 39	15 to 36
Pretreatment ΔE					
Median	15.3	15.2§	13.4	15.4	14.9
Interquartile range	12.4 to 18.6	12.3 to 19.5	7.5 to 17.9	12.5 to 17.7	12.2 to 17.0
ΔE after five treatments					
Median	8.5	8.9¶	6.6	7.5	7.5
Interquartile range	6.2 to 11.9	6.5 to 12.4	4.6 to 13.9	5.1 to 11.2	7.2 to 11.3
Original effect of treatment‖					
Median	−5.9	−5.7	−3.8	−6.4	−5.7
Interquartile range	−8.6 to −3.2	−8.1 to −3.0	−6.1 to −2.7	−9.1 to −3.3	−7.8 to −4.1
ΔE at 9.5-yr follow-up					
Median	—	12.4§¶	11.7	—	—
Interquartile range	—	8.7 to 14.8	7.6 to 20.2	—	—
Change in ΔE at follow-up**					
Median	—	2.5	2.0	—	—
Interquartile range	—	−0.1 to 5.5	0.7 to 8.4	—	—

* ΔE denotes the difference in color between the port-wine stain and normal skin. The Wilcoxon signed-rank test was used to determine the statistical significance of changes in ΔE over time.
† Six patients received five treatments, had their skin color measured, and did not receive any additional treatments.
‡ Ten patients were excluded because they received treatment elsewhere after receiving five treatments in the study hospital. Six of these patients received additional laser treatments and four received medical tattoos.
§ $P<0.001$, indicating a significant persistent current effect (a decrease in ΔE) of pulsed-dye–laser treatment as compared with the pretreatment measurement.
¶ $P=0.001$, indicating significant redarkening of the stains (an increase in ΔE) between the measurement taken after the first five treatments and the follow-up measurement.
‖ The original effect of treatment is the color measurement obtained after the first five treatments minus the color measurement at baseline; negative values indicate a decrease in ΔE.
** The change in ΔE at follow-up is the 9.5-yr follow-up measurement minus the measurement taken after the first five treatments; positive values indicate an increase in ΔE.

did not reply. An additional 10 patients were excluded from the study because they had been treated outside the study hospital between the time of the last color measurement obtained after five treatments and the follow-up study (subgroup 2 in Table 1). Of these 10 patients, 6 had received laser treatments and 4 had received medical tattoos. Thus, 51 of the original 89 patients (57%) were included in the follow-up study. These 51 patients did not differ significantly from the original 89 patients with respect to age, baseline color measurements, color measurements obtained after an average of five treatments, or original effect of treatment (color measurements obtained after the first five treatments minus baseline color measurements) ($P>0.50$ by the Wilcoxon signed-rank test).

After completing five treatments and having their skin color measured in the previous study, 45 of the 51 patients included in the present study had additional treatment sessions in our hospital. In these sessions, either all or part of the stain was treated with the same laser and the same methods used in the previous treatments. The median duration of the original five-treatment regimen for the 51 patients was 1.9 years (interquartile range,

1.4 to 2.4). The median number of additional sessions was 7 (interquartile range, 3 to 13; range, 1 to 39), and the median duration of the additional treatment regimen was 3.9 years (interquartile range, 1.1 to 5.4). The median time between the last treatment session and the follow-up measurement was 5.8 years (interquartile range, 4.1 to 8.9). The median time between the measurement obtained after the first five treatments and the follow-up measurement was 9.5 years (interquartile range, 9.2 to 10.1). Thus, the median duration of follow-up in this study was 9.5 years.

COLOR MEASUREMENTS

The color measurements are summarized in Table 1. The median ΔE increased significantly from 8.9 (interquartile range, 6.5 to 12.4) after the first five treatments to 12.4 (interquartile range, 8.7 to 14.8) at a median of 9.5 years of follow-up ($P=0.001$). However, the median ΔE was still significantly lower at follow-up (12.4; interquartile range, 8.7 to 14.8) than before laser treatment (15.2; interquartile range, 12.3 to 19.5; $P<0.001$), indicating a persistent effect of pulsed-dye–laser treatment. Figure 1 illustrates the results by including recent photographs of the patients along with the illustrations used in the previous publication.

Of the 51 patients evaluated, only 6 (2 men and 4 women) did not receive treatment after the first five treatments; the results from these patients represent true follow-up results after treatment (subgroup 1 in Table 1). In all six of these patients, the value of ΔE was higher at follow-up than after the five treatments; the increases in ΔE were 0.2, 0.9, 1.3, 2.8, 6.8, and 13.1.

QUESTIONNAIRE

Of the 51 patients evaluated, 30 (59%) were satisfied with the result of the pulsed-dye–laser treatment (including any treatment sessions subsequent to the measurement made after the first five treatments). The remaining 21 (41%) were not satisfied. Three patients (6%) reported that their stains had become lighter since their last treatment session, 18 (35%) reported that they had become darker, and the remaining 30 (59%) thought that they had not changed in color.

For the three patients who reported that their stains had become lighter, the changes in ΔE from the measurements made after the first five treatments to follow-up (i.e., the measured changes in the color of the stain over the previous 9.5 years) were –2.0, 1.1, and 1.7. The mean (±SD) change in ΔE was 1.6±4.7 (range, –10.7 to 7.5) for the 30 patients who considered their stains unchanged and 3.4±4.5 (range, –4.9 to 13.1) for the 18 patients who reported that their stains had darkened.

DISCUSSION

This follow-up study used objective color measurements to assess the long-term efficacy of pulsed-dye–laser treatment of port-wine stains. The results show that the median ΔE (the difference in color between the stain and normal skin) increased from 8.9 to 12.4 at a median of 9.5 years after the last of five treatments of the complete stain, although the patients had received a median of seven additional laser treatment sessions after the initial five treatments. However, the follow-up ΔE was still lower than the pretreatment value (12.4 vs. 15.2). From these results, it can be concluded that the positive effect of five treatments is not completely durable and that significant redarkening occurs at long-term follow-up.

The results of this study confirm previous anecdotal reports of the recurrence of port-wine stains after pulsed-dye–laser treatment. However, the previous reports were all based on questionnaires presented to the patients or treating physicians and show widely varying outcomes. Orten et al.[5] reported a 50% recurrence rate of port-wine stains 5 years after treatment, and Mork et al.[6] reported a recurrence rate of 11% "several" years after treatment. Michel et al.,[3] in a study investigating the effect of age at treatment on recurrence (at least 1 year after completion of treatment), found redarkening in 16% of patients. The authors found no correlation between the rate of recurrence and the duration of follow-up, indicating that recurrence may be mainly related to individual patient characteristics. Ho et al.[7] investigated the effect of laser treatment in Chinese patients and surprisingly found no recurrence after a mean follow-up of 3.4 years. Finally, in a study by Hansen et al.,[4] 19% of patients reported recurrence of color at 7 years of follow-up.

In our study, even though 45 patients received additional treatment sessions, the ΔE of the whole group had increased at 9.5 years of follow-up. Only six patients did not receive more than five treatments. Among these patients (subgroup 1 in Table 1), the effect of five treatments of the com-

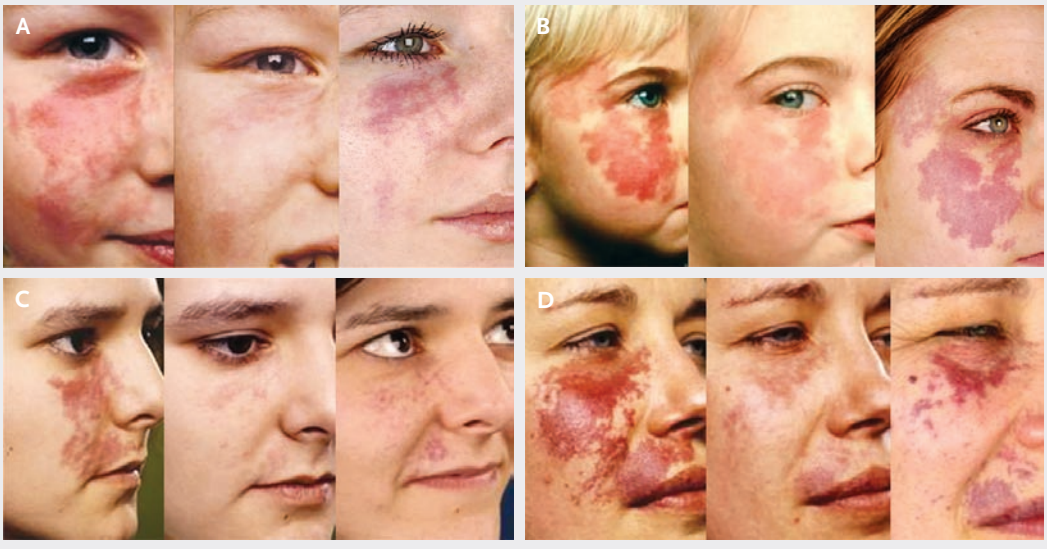

Figure 1. Redarkening of Port-Wine Stains after Pulsed-Dye–Laser Treatment.

Recent photographs of the patients are included, along with the illustrations used in the previous study.[9] Each panel shows a patient before treatment (left), after six treatments of the complete port-wine stain (middle), and at follow-up 9 years (Panel A) or 10 years (Panels B, C, and D) after five treatments (right). In all four patients, redarkening of the stain can be observed when the right-hand photograph is compared with the middle photograph.

plete port-wine stain was smaller than the effect of treatment in the entire group; the change in ΔE was −3.8 in subgroup 1 and −5.7 in the entire group. The amount of redarkening at 9.5 years of follow-up was also somewhat smaller in subgroup 1 than in the entire group (change in ΔE, 2.0 vs. 2.5); however, the small number of patients precludes drawing conclusions.

There is no consensus on the mechanism of redarkening, although it has been widely discussed. Several mechanisms may contribute. First, it has frequently been hypothesized (but rarely objectively shown) that untreated port-wine stains darken with age.[11] Natural darkening with age, possibly resulting from progressive ectasia of the remaining vessels, may have a role in the redarkening of incompletely eradicated port-wine stains. Support for this hypothesis includes our observation that redarkening occurred in all six patients who did not receive additional treatment after the first five treatments. Second, neovascularization resulting from post-treatment thrombus formation[12] and angiogenesis of capillary structures from deeper parts of the port-wine stain (which are untreatable with the pulsed-dye laser because of its limited penetration depth) may also contribute to long-term redarkening of the stain. All these mechanisms — progressive ectasia, neovascularization resulting from thrombus formation, and angiogenesis from remaining parts of the stain — support the hypothesis that the cause of port-wine stains is the lack of surrounding neurons regulating blood flow through the ectatic postcapillary venules.[13,14] Since pulsed-dye–laser treatment obviously does not increase neural control, both newly formed and persistent vessels would suffer from the same lack of neural control.

Two final points should be mentioned concerning the possible mechanism of redarkening. First, we assessed only color, whereas other characteristics of port-wine stains, such as size, surface structure, and hypertrophy,[15] may also have a role in recurrence. Second, several changes in treatment (the use of longer wavelengths, greater pulse energies, larger spot size, and cryogen spray cooling) have been implemented in new generations of pulsed-dye lasers since the treatment of our patients with the Candela SPTL-1. Whether treatment of port-wine stains with these new lasers will reduce the incidence of redarkening at long-term follow-up remains to be investigated.

Fifty-nine percent of the 51 patients who un-

derwent follow-up measurements were satisfied with the results of the treatment. On the other hand, 10 of the original 89 patients (11%) sought additional treatment (laser treatments or medical tattoos) outside our hospital. In these patients (subgroup 2 in Table 1), the original port-wine stain was not darker (i.e., the pretreatment ΔE was not higher) than in the rest of the patients, nor was the effect after five treatments lower. These results indicate that the patients did not seek additional treatment because their treatment results were worse than average.

In the three patients who reported that their stains had become lighter, the changes in color measurements were small but variable, whereas patients who considered their stains to be either unchanged or darker had an increase in ΔE. Thus, patients seem to underestimate the changes in color taking place in their stains, probably because the changes occur slowly over several years, making detection difficult. The discrepancies between the perceptions of the patients and color measurements emphasize the importance of using objective assessment instead of patient or physician questionnaires when assessing the long-term results of treatment of port-wine stains. Furthermore, although histopathological data are available from untreated port-wine stains,[16] obtaining such data from treated port-wine stains is virtually impossible because very few patients will consent to repeated biopsies of their stains. Therefore, color measurement is currently the most objective method of assessing changes in port-wine stains after treatment.

In conclusion, although pulsed-dye–laser therapy remains the gold standard for the treatment of port-wine stains and has a persistent beneficial effect, the current study objectively shows that redarkening occurs at long-term follow-up. Therefore, we recommend that before commencing pulsed-dye–laser therapy, all patients should be informed of the possibility of redarkening of the stain after treatment.

No potential conflict of interest relevant to this article was reported.

We thank A.J. Leijen for her important contribution in tracing and contacting the patients and D. Ubbink for his assistance in data analysis.

REFERENCES

1. Tan OT, Sherwood K, Gilchrest BA. Treatment of children with port-wine stains using the flashlamp-pulsed tunable dye laser. N Engl J Med 1989;320:416-21.

2. Ozluer SM, Barlow RJ. Partial re-emergence of a port-wine stain following successful treatment with flashlamp-pumped dye laser. Clin Exp Dermatol 2001;26:37-9.

3. Michel S, Landthaler M, Hohenleutner U. Recurrence of port-wine stains after treatment with the flashlamp-pumped pulsed dye laser. Br J Dermatol 2000;143:1230-4.

4. Hansen K, Kreiter CD, Rosenbaum M, Whitaker DC, Arpey CJ. Long-term psychological impact and perceived efficacy of pulsed-dye laser therapy for patients with port-wine stains. Dermatol Surg 2003;29:49-55.

5. Orten SS, Waner M, Flock S. Port wine stains: an assessment of 5 years of treatment. Arch Otolaryngol Head Neck Surg 1996;122:1174-9.

6. Mork NJ, Austad J, Helsing P. Do port wine stains recur after successful treatment with pulsed dye laser? J Eur Acad Dermatol Venereol 1998;11:S142-S143.

7. Ho WS, Chan HH, Ying SY, Chan PC. Laser treatment of congenital facial port-wine stains: long-term efficacy and complication in Chinese patients. Lasers Surg Med 2002;30:44-7.

8. Troilius A, Wrangsjo B, Ljunggren B. Patients with port-wine stains and their psychosocial reactions after photothermolytic treatment. Dermatol Surg 2000;26:190-6.

9. van der Horst CMAM, Koster PHL, de Borgie CAJM, Bossuyt PMM, van Gemert MJC. Effect of timing of treatment of port-wine stains with the flash-lamp–pumped pulsed-dye laser. N Engl J Med 1998;338:1028-33.

10. Brainard DH. Colorimetry. In: Bass M, van Stryland EW, Williams DR, Wolfe WL, eds. Handbook of optics. Vol. 1. New York: McGraw-Hill, 1995:26.26-26.38.

11. Tan OT. Pulsed dye laser treatment of adult port-wine stains. In: Tan OT, ed. Management and treatment of benign cutaneous vascular lesions. Philadelphia: Lea & Febiger, 1992:83-99.

12. Heger M, Beek JF, Moldovan NI, van der Horst CMAM, van Gemert MJC. Towards optimization of selective photothermolysis: prothrombotic pharmaceutical agents as potential adjuvants in laser treatment of port wine stains. Thromb Haemost 2005;93:242-56.

13. Rosen S, Smoller BR. Port-wine stains: a new hypothesis. J Am Acad Dermatol 1987;17:164-6.

14. Breugem CC, Hennekam RCM, van Gemert MJC, van der Horst CMAM. Are capillary malformations neurovenular or purely neural? Plast Reconstr Surg 2005;115:578-87.

15. Koster PHL, Bossuyt PMM, van der Horst CMAM, Gijsbers GHM, van Gemert MJC. Characterization of portwine stain disfigurement. Plast Reconstr Surg 1998;102:1210-6.

16. Barsky SH, Rosen S, Geer DE, Noe JM. The nature and evolution of port wine stains: a computer-assisted study. J Invest Dermatol 1980;74:154-7.