Changes in Skin Redness, Pigmentation, Echostructure, Thickness, and Surface Contour After 1 Pulsed Dye Laser Treatment of Port-wine Stains in Children

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Background: The pulsed dye laser is the treatment of choice for children with port-wine stains (PWSs). Evaluation of treatment outcome and adverse effects is traditionally based on subjective clinical scoring systems. We intend to objectify treatment results and adverse reactions after 1 treatment with the pulsed dye laser.

Design: A before-and-after trial using skin reflectance to detect changes in skin redness and pigmentation, ultrasonography to evaluate changes in echostructure and skin thickness, and 3-dimensional surface contour analysis to detect changes in surface texture.

Patients: Twelve children with PWSs.

Setting: A university dermatological department.

Results: The skin reflectance–determined change in skin redness correlated with the clinical response \( (r=0.46, P<.002) \). The percentage of reflectance-determined lightening was equal for pink, red, and dark red PWSs (median, 42.9%). Skin pigmentation increased after laser treatment \( (P<.007) \). Ultrasonography revealed lower dermal echogenicity of preoperative PWSs than of postoperative PWSs \( (P<.007) \) and healthy skin \( (P<.001) \). An increase in echogenicity reflected a decrease in the dermal water (blood) content. Variations were found in the dermal localization of the PWS. Skin thickness was significantly higher in the PWS before treatment than after \( (P<.001) \). The preoperative lesional thickness correlated inversely with the ultrasound-assessed treatment response \( (r=0.35, P<.04) \). The surface contour parameters decreased significantly after laser treatment, indicating a flattening of the skin surface. The contour changes correlated positively with treatment response. By clinical evaluation, no hypopigmentation or texture changes were detected.

Conclusion: The evaluation of treatment outcome and adverse effects is refined by the use of skin reflectance, ultrasonographic, and surface contour analysis.

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PORT-WINE STAINS (PWSs) are congenital vascular malformations characterized by ectatic capillary and venule-sized vessels in the papillary and upper reticular dermis. These birthmarks occur in approximately 0.3% of neonates and most commonly involve the face and neck.\(^1\) Use of the pulsed dye laser (PDL) has dramatically improved the treatment of patients with PWS and today is considered the treatment of choice for PWSs in the pediatric population.\(^2,3\)

The efficacy of the PDL is reported to be associated with the anatomical location of the PWS and the number of treatment sessions\(^4,7\); however, diverging results have been published about the importance of the color of the PWS\(^8,9\) and the age of the child.\(^5,6,10,11\) For the individual child, the treatment outcome is unpredictable because an indefinable subgroup of children responds slowly and with poor outcome.\(^7,11\) However, half of the children overall achieve about 75% blanching after 2 to 3 PDL treatments.\(^2,6\) The incidence of adverse effects is generally considered low for PDL treatment of patients with PWSs.\(^13\) Nevertheless, it has been suggested recently that the incidence may be higher than previously stated in the literature.\(^14\)

The evaluation of treatment outcome and adverse effects with PDL treatment is traditionally based on subjective clinical scoring systems and less frequently on objective techniques, of which standardized photography and reflectance spectrophotometry are reported to be suitable methods.\(^12,15\) It is important to objectify the treatment response and the presence of adverse reactions for several reasons: for comparing treatment outcomes, for defining the optimal physical

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PATIENTS, MATERIALS, AND METHODS

PATIENTS

Twelve consecutive patients aged 2 to 11 years (mean age, 5 years) with macular PWSs were enrolled in the study from October 1995 to February 1996. Informed consent was given by their parents after the nature of the procedures had been fully explained. The lesions were previously untreated and mainly located on the face (11 patients with facial lesions and 1 patient with PWSs on the lower extremity). Eleven patients were white and 1 was Mongoloid; 8 patients were girls and 4 were boys. None were suntanned. During the laser treatments, the children were under general anesthesia with a combination of halothane, nitrous oxide, and oxygen. Three patients with pink PWSs, 5 patients with red PWSs, 3 patients with dark-red PWSs, and 1 patient with purple PWSs were included.

LASER TECHNIQUES

A commercially available flashlamp-pumped PDL (Candela SPTL-1b, Candela Corp, Wayland, Mass) with a wavelength of 585 nm±5 nm and a pulse duration of 450 microseconds was used. Spot diameter was 7 mm, and test areas (n=43) were exposed to 4 slightly overlapping pulses (n=35) or 8 overlapping double pulses (n=8). Each patient was exposed on 1 to 5 test areas, the number depending on the size of the lesion and the applied fluences depending on the age of the child. In general, younger patients were treated with the lowest energy densities. Test areas were placed in lesion sites of uniform appearance to diminish intralesional variations in the PWS. The energy densities ranged between 3.25 and 6.25 J/cm², with 0.75-J/cm² increments. An external pyroelectric energy meter (Ophir PE50-DIF, Ophir Optronics Inc, Peabody, Mass) calibrated to ±3% was used to monitor fluences.

Assessment of adverse reactions included clinical evaluation, skin reflectance to objectify pigmentary changes, and surface contour analysis to objectify surface texture changes. Laser settings for the individual patient without occurrence of adverse reactions, and, moreover, for guiding the patient and the physician in establishing the moment when further treatment sessions are without additional benefit to the patient.

The aim of the present study was therefore to objectify treatment results and adverse reactions after 1 PDL treatment of children with PWSs using noninvasive techniques such as skin reflectance for detection of blanching and pigmenary changes, ultrasonography for evaluation of echostructure and skin thickness changes, and 3-dimensional surface contour analysis for detection of surface texture changes.

RESULTS

The response to treatment and adverse reactions were evaluated 12 weeks after PDL treatment. Treatment response was determined by clinical evaluation, by skin reflectance–evaluated blanching, and by ultrasonographic evaluation of echostructure and skin thickness. Assessment of adverse reactions included clinical evaluation, skin reflectance to objectify pigmentary changes, and surface contour analysis to objectify surface texture changes.

TREATMENT RESPONSE

Clinical Evaluation

The median percent lightening of test areas was 40%, with a 25th percentile of 0% and a 75th percentile of 60%. Overall, 10 (23%) of 43 test areas showed more than 70% lightening after 1 PDL treatment. Ten test areas were pink (23% of total), 17 were red (40%), 12 were dark red (28%), and 4 were purple (9%). The median clearance percent (with 25th and 75th percentiles in parentheses) was 0% (0% and 0%) for pink lesions, 40% (30% and 60%) for red lesions, 65% (45% and 70%) for dark red lesions, and 15% (7.5% and 20%) for purple lesions, the clearance for
Skin Reflectance

Skin redness and skin pigmentation were measured independently before and 12 weeks after laser treatment by skin reflectance (UV-Optimize, Matic, Herlev, Denmark). The equipment uses 555- and 660-nm wave bands of light in which the discrimination between light absorption in melanin and hemoglobin is maximal. Skin pigmentation and redness are quantified independently and continuously on relative scales from 0% to 100%.17 Zero percent pigmentation is found in white skin with no pigment at all, and 100% corresponds to the pigmentation in theoretically absolutely black skin with no light reflection. Zero percent skin redness corresponds to skin in which blood has been temporarily drained from the area; 100% redness corresponds to highly vascular skin with a dark bluish red PWS.

Ultrasonography

Cross-sectional B-mode scans of the skin were obtained with a 20-MHz ultrasonograph (Dermascan C, Cortex Technology, Hadsund, Denmark).18 The gain compensation curve was adjusted in the oblique position at 14 to 49 dB.19,20 The transducer has a resolution of 130×60 μm. The velocity of ultrasound in the skin is 1380 m/s. The ultrasonic wave is partially reflected at the boundary between adjacent structures and generates echoes of different amplitudes. The amplitudes of echoes of single image elements (pixels) are ascribed to a numeric scale (0-255). The low echogenic pixel (LEP) range extends from 0 to 30. Changes in LEP counts are considered to reflect changes in dermal water content19,20 in this study, probably reflecting changes in the blood content in the dilated vascularity of the PWS lesion. In each image, the number of LEPs and total echogenic pixels (TEPs) was measured and a ratio (LEP: TEP) was calculated to compensate for differences in skin thickness. Pixels were measured within the dermal region, extending from the epidermal entrance echo to the interface between skin and subcutaneous tissue (Figure 1). In addition, skin thickness (expressed in millimeters) was measured as an average of all A-scan contributing to B-mode image, corresponding to the distance from the epidermal entrance echo and the interface between the skin and subcutaneous fat. Because ultrasonography is not an objective measurement, the image analysis was performed in a blinded fashion without access to patient data.

3-Dimensional Surface Contour Analysis

A total of 96 silicone replicas were obtained before and 12 weeks after surgery (Silflo, Flexico, Heris, England). The replicas were scanned by a laser-optical profilometer equipped with an optical triangulation sensor and operating with a sample density of 25 points per millimeter (UBM Messtechnik GMBH, Ettlingen, Germany). The measuring area could be identified with an accuracy of 40 μm. Skin surface topography was described by means of 3-dimensional parameters, which give more detailed information compared with the previously used 2-dimensional parameters. The interdependent amplitude parameters Sₐ (the arithmetic mean deviation) and S₈ (the root mean square of Sₐ) describe the average deviation of the profile from the mean line and give a first impression of the average roughness. S₉ represents the height of the core material portion, ie, Sk the bearing area, Sₐₖ and S₈ₖ the surface valley proportion and surface peak proportion, respectively, representing the material below and above the core surface.21

Statistics

We used nonparametric statistics to present our data. Consequently, medians with 25th and 75th percentiles are given for descriptive statistics. The Wilcoxon rank sum test was used for paired comparisons before and after treatment and the Mann-Whitney U test was used for nonpaired comparisons. Comparisons were based on test areas, since it was not possible to separate the interindividual and individual variation from the data composition. The median number of test areas per patient was 3.5 (range, 1-5 test areas), thereby eliminating dominance from a few individuals. Correlations were derived from the Spearman rank correlation coefficients and their corresponding P values; P≤.05 was considered significant.

Skin reflectance determined degree of lightening correlated significantly to the clinically assessed treatment response (Figure 2). We found the following median (25th and 75th percentile) values within the different response categories: 5% (1% and 7%) in the no response group, 11% (1% and 15%) in the the poor response group, 8% (6% and 11%) in the moderate response group, and 12% (10% and 13.5%) in the good response group. Differences were significant between the no response and the moderate and good response groups (P<.02). No comparisons with the poor result group were significant, which may be ascribed to the larger variance found in this group. The degree of lightening (median; 25th and 75th percentiles) was found to be significantly lower in pink lesions (4.5%; 0% and 6%) than in red (8.6%; 7% and 11.7%) and dark red (11.5%; 8% and 14%) lesions (P<.001). Purple lesions had low clearances as well (1%; 1% and 7%); however, they were not significantly different from those of the red and dark red lesions. Nevertheless, the percentage of lightening in proportion to the preoperative lesional color (redness %preoperative – redness %postoperative) / (redness %preoperative × 100) was not signifi-

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cantly different for pink, red, and dark red lesions (median, 42.9%), whereas the percentage of lightening was significantly lower for purple lesions (median, 6.3%) compared with red lesions (median, 40.0%) \((P<.04)\).

### Ultrasonography

Dermis and adjacent epidermis was identified as the space between the epidermal entrance echo and the interface with the hypoechogenic subcutaneous tissue (Figure 1). The values of LEP:TP were significantly higher before than after treatment in the PWS lesions, and PWS had higher values of LEP:TP than the surrounding healthy skin, indicating that the echogenicity of laser-treated skin approaches the echogenicity of healthy skin (Figure 1). Treatment response was calculated as the change in echogenicity by subtracting the 3-month LEP:TP from the pretreatment LEP:TP. There was no correlation between the change in echogenicity and the clinically assessed treatment response, not even when the ultrasound-assessed treatment response was corrected for the healthy skin echogenicity. No relation to the initial lesion color could be detected. Ultrasound scans showed variability in the localization of the PWS in the dermis. Some PWSs were located superficially, mainly in the papillary dermis \((n=2)\), others were deeper in the reticular dermis \((n=5)\), and still others were spread all over the entire dermis \((n=5)\). It was not possible to correlate the dermal location of the nevus with the clinical effect of the treatment due to a small number of the different lesion types.

Median values of skin thicknesses were significantly higher in PWSs before treatment, 1.00 mm \((0.92-1.13\) mm\) than after treatment, 0.95 mm \((0.90-1.05\) mm\) \((P<.001)\). Untreated control skin thickness remained constant \((median, 0.88\ mm; 0.84-0.96\ mm)\). Port-wine stain lesions were thicker than the surrounding healthy skin before \((P=.09)\) and after \((P<.05)\) treatment. Skin thickness before treatment correlated inversely with the ultrasound-assessed treatment response when it was corrected for the healthy skin echogenicity \((r=0.35, P<.04)\).
ADVERSE REACTIONS

Clinical Evaluation

One patient with a PWS at the lower extremity developed hemosiderinlike hyperpigmentation in 2 test sites. No patients developed hypopigmentation, epidermal alterations, atrophy, or hypertrophy.

Skin Reflectance

The pigmentation in PWS skin was corrected for acquired variations in pigmentation due to sun exposure during the observation period by subtracting the pigmentation of the surrounding healthy skin. These corrected pigmentation percentages were slightly but significantly higher after laser treatment (median, 2%; 0% and 5%) than before (median, 1%; −3% and 3%) (P<.007). In 29 (67%) of 43 test sites this reflectance-evaluated hyperpigmentation could be established.

3-Dimensional Surface Contour Analysis

The surface contour parameter values decreased after surgery, indicating a flattening of the skin surface texture after laser treatment (Figure 3). Significantly lower values were found for Sa (P<.006), Sc (P<.005), Sg (P<.009), and Svh (P<.02); Svk followed the same trend but was not significant (P=.10). There was no dose-response relationship between the applied laser doses and the degree of surface changes. The changes in Sa, Sc, and Sg correlated positively with the clinically evaluated treatment response (r values were between 0.41 and 0.45; P<.008) and the reflectance-evaluated treatment response (r values were between 0.35 and 0.37; P<.03) (Figure 4). Changes in Svk and Svh did not correlate with treatment response in a consistent way. Treatment response evaluated with ultrasound did not correlate with the change in surface parameter values. The pretreatment surface contour parameters did not correlate consistently with the treatment outcome assessed by clinical examination, skin reflectance, and ultrasonography.

This is the first study that (1) applies ultrasonography in the assessment of treatment results from the PDL and (2) documents the presence of subclinical adverse effects using skin reflectance and surface contour analysis. The results provide information about the effects on skin redness, pigmentation, echostructure, thickness, and surface contour after 1 treatment with the PDL of PWS in children, not after treatment to maximal clearing.

We found that clinical response, assessed by photographic documentation, correlated acceptably with the skin reflectance–evaluated lightening, which is in accordance with the results reported by Troilius and Ljunggren.12 However, we did not find any association between the change in echogenicity and the degree of lightening. This lack of correlation may be ascribed to the fact that different parameters are evaluated by the methods: ultrasonography evaluates the echogenicity in the superficial and deep skin layers, whereas clinical evaluation and skin reflectance predominantly determine the superficial skin redness. The missing correlation may, moreover, be due to methodical problems, ie, error is introduced when the results from the noninvasive methods are related to and correlated with the highly subjective semiquantitative clinical evaluation that is often considered the standard. Nevertheless, the semiquanti-
been used previously as the basis for drawing conclusive clinical evaluation facilitates data analysis and has been used previously as the basis for drawing conclusions.\textsuperscript{11,16} Furthermore, a precise relocation of the treated areas, a precise placement of the ultrasonic probe, and variations in blood flow and dermal water content may constitute important factors. All preoperative and postoperative measurements were performed when the children were given general anesthesia. In an attempt to correct for the anesthesia-induced cutaneous vasodilatation, we subtracted the echogenicity of the surrounding healthy skin in the same way as the reflectance-detected redness degree were corrected for the healthy skin values. However, contrary to the skin reflectance measurements, no advantage was obtained by correcting for the vascular fluctuations, indicating that general anesthesia was of no or minor importance to the ultrasonographic measurements. Therefore, we decided to present the ultrasonographic measurements as uncorrected values, although the reflectance-detected blanching was presented as a corrected redness degree. Nevertheless, the echogenicity expressed as the ratio LEP:TP was significantly higher in PWSs before than after PDL treatment, indicating an increase in dermal echogenicity after treatment; thus, quantification of treatment results was possible.

We examined the skin carefully and found only a few areas with hemosiderinlike hyperpigmentation. No hypopigmentation, epidermal shiny appearance, atrophy, or hypertrophy was seen. Nevertheless, the applied objective methods demonstrated an increase in skin pigmentation and a flattening of the skin structure after 1 treatment with the PDL, indicating that skin reflectance and surface contour analysis are able to distinguish minor, subclinical adverse reactions. In this study, we classified any change in the surface contour as an adverse effect because all PWS lesions were in children and had a regular surface texture that macroscopically resembled the adjacent, healthy skin structure. However, skin flattening may not always be an adverse reaction because the skin texture of a mature PWS often is slightly raised and irregular. In this case, flattening would be a positive therapeutic response. Minor surface flattening in this study is associated with the degree of treatment response, suggesting that only fluence levels that produce some subclinical flattening induce a lesional response.

It may provide important clinical information to the laser surgeon that we have documented the presence of subclinical adverse reactions. These subclinical adverse effects may indicate that clinically visible adverse effects will be induced if higher fluence levels are applied to the PWS. The energy range in this study (3.25-6.25 J/cm\textsuperscript{2}) is, nevertheless, in the low range of the conventional fluence levels used to treat patients with PWSs, making this study even more clinically relevant. However, our results confirm results from previously published articles\textsuperscript{7,9,11,22} reporting that PDL treatment is associated with a low incidence of clinically visible adverse effects. A study\textsuperscript{13} designed to assess the incidence of adverse reactions with PDL treatment established that the incidence of complications is low. Hypertrophy occurred in 0.0% of the treated patients, atrophy in 0.1%, hypopigmentation in 2.6%, and hyperpigmentation in 1.0\%.\textsuperscript{22} However, a recent report demonstrated a higher percentage of adverse effects, especially hyperpigmentation (27\%),\textsuperscript{19} and because these results are in accordance with those of other previous reports, the question is raised whether adverse effects occur more commonly than traditionally reported.\textsuperscript{6,14,23}

We found that the percentage of skin reflectance-determined lightening in proportion to the preoperative lesional color was equal for pink, red, and dark red PWS lesions, whereas the absolute reflectance-determined degree of clearance was associated with the color of the untreated lesion, pink lesions responding with the lowest degree of lightening. This finding may indicate a tendency to underestimate the clinically evaluated treatment response in patients with pink PWSs. Controversies have been reported concerning the importance of preoperative lesional color for the treatment outcome: Fitzpatrick et al\textsuperscript{9} reported that the highest clearance is produced in pink lesions and the lowest clearance in purple lesions when the PDL is used at 585 nm; however, no statistical calculations were performed in this study. On the other hand, a recently published study demonstrated that pink lesions respond with poor clearance due to small-diameter vessels (mean diameter, 16.5 \textmu m) and, moreover, that pink and purple lesions consist of deeply located vessels, associating these lesions with a negative outcome.\textsuperscript{10} The variations in treatment response with the PDL may be caused by interindividual and intraindividual heterogeneity of the PWS with regard to lesion depth and vessel diameter. Consequently, the concept of selective photothermolysis is fulfilled to a variable degree, and residual vessels may persist if the vessels lie beyond the limited penetration depth of 1.2 mm from the dermoepidermal junction.\textsuperscript{24,25} These considerations are supported by the fact that the mean depth of vessels has been associated with clinical response and appointed as a main prognostic factor.\textsuperscript{7} We therefore related the preoperatively ultrasound-evaluated lesional thickness to treatment response and found that lesional thickness correlated inversely with the ultrasound-assessed treatment response ($r=0.35$, $P<.04$). How-

Figure 4. A representative example of the relation between skin reflectance-evaluated lightening and skin surface contour changes: $S_a$ (arithmetic mean deviation) before treatment $- S_c$ (arithmetic mean deviation) after treatment. A trend line is illustrated, although statistical calculations are nonparametric.
ever, no association was seen with clinical response or reflectance-evaluated treatment response, again pointing out that ultrasonography evaluates parameters different than skin redness. Nevertheless, the finding supports the idea that vessel depth and lesion thickness are important to the treatment outcome.

This study demonstrates the possibility of using ultrasonography to quantify the echostucture in patients with PWS before and after PDL treatment and that the evaluation of treatment outcome and adverse reactions may be improved and refined by skin reflectance, ultrasonographic, and surface contour analysis. Consequently, these objective values may guide the patient and the physician in establishing further treatment procedures.

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