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Use of Erythema Index Imaging for Systematic Analysis of Port Wine Stain Skin Response to Laser Therapy

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Background and Objectives: Quantitative methods to assess port wine stain (PWS) skin response to laser therapy are needed to improve therapeutic outcome. In this study, PWS skin erythema was analyzed using erythema index difference (ΔEI: erythema index difference between PWS and normal skin) images before and after treatment to investigate systematically subject-dependent response to laser therapy.
Study Design/Materials and Methods: Cross-polarized digital skin color images were acquired from 17 subjects with facial PWS and the associated ΔEI images were computed. Qualitative and quantitative analyses of PWS skin erythema were performed with ΔEI images, in which ranges of 40–6 and 5–0 represented PWS and normal skin, respectively.
Results: After laser therapy, we qualitatively observed *a reduction in the ΔEI values for all subjects*. Regression fitting of ΔEI values before and after PWS laser therapy was associated with strong positive linear correlation.
Conclusions: The imaging modality and analysis method allowed systematic analysis of *PWS skin erythema* in response to laser therapy. PWS skin response was dependent on pretreatment ΔEI values, suggesting that erythema can be utilized as an effective *parameter* to *monitor* PWS *response* to laser therapy. Lasers Surg. Med. 37:186–191, 2005. © 2005 Wiley-Liss, Inc.

Key words: cross-polarized color image; dermatology; image analysis; laser therapy; port wine stain

INTRODUCTION

Port wine stains (PWS) are congenital hypervascular cutaneous malformations that occur typically on the face and neck with a prevalence of 0.3–0.5% [1,2]. The pulsed dye laser (PDL) is considered the treatment modality of choice for the clinical management of PWS patients [3–6]. To destroy PWS blood vessels irreversibly, PDL ($\lambda = 585$–600 nm) light is preferentially absorbed by hemoglobin in the ectatic capillaries. There, the radiant energy is converted to heat causing thermal damage and thrombosis in the targeted PWS blood vessels. However, the success rate for achieving complete PWS blanching is less than 10%, even after multiple laser treatments [7].

PWS skin response to laser therapy is dependent on several factors, such as the geometric pattern of capillary ectasia [8], vessel depth and diameter [9,10], blood volume fraction [11], and relative concentration of competing chromophores (e.g., melanin) within the skin [12]. Several noninvasive techniques, such as colorimetry, reflectance spectrophotometry, and laser Doppler flowmetry, have been used to quantify such factors [13]. However, these techniques are not accepted as clinically practical methods for evaluation due to the difficulty in obtaining repeatable and reproducible measurements of PWS skin. Therefore, there is a need to develop new modalities that can be easily utilized in the clinic to monitor PWS laser therapy.

Recently, skin color images have been used to predict and evaluate PWS skin response to laser therapy [14–17]. In a previous study [14], we utilized cross-polarized skin color images to quantitatively characterize PWS skin. Therein, a* images from the Commission Internationale de l'E'clairage (CIE) L*a*b* color space were computed from cross-polarized color images and used as an indicator of PWS skin erythema. However, a recent study suggested that a* values may be affected by epidermal melanin content [18]. In the present study, to minimize the corruption of erythema measurements by epidermal melanin, we instead computed erythema index difference (ΔEI) image, which allows qualitative and quantitative analyses of PWS skin erythema. Using this information, the aim of this study is to demonstrate the feasibility of using ΔEI imaging as a predictive factor of PWS response to laser therapy.

MATERIALS AND METHODS

Cross-Polarized Skin Color Imaging System

The employed system is identical to that described previously [14]. Briefly, the imaging system is based on a

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digital color camera (Model DiMAGE7, Minolta Co., Osaka, Japan) equipped with a ring flash for consistent uniform illumination. Cross-polarized optics were incorporated into the system to remove surface glare, which corrupts subsurface color information. To eliminate artifacts induced by environmental lighting, patient images were acquired in a dark room.

To ensure that measurement sites on the face were available in a reproducible manner, a custom head-positioning device was constructed and placed within the working distance of the ring flash, resulting in uniform illumination [14]. Facial images of PWS patients were obtained at an optimal view angle that minimizes non-uniform illumination on the region of interest due to facial curvature [19]. Figure 1 *shows the imaging system* (Figure 1a) *and custom head-positioning device* (Figure 1b).

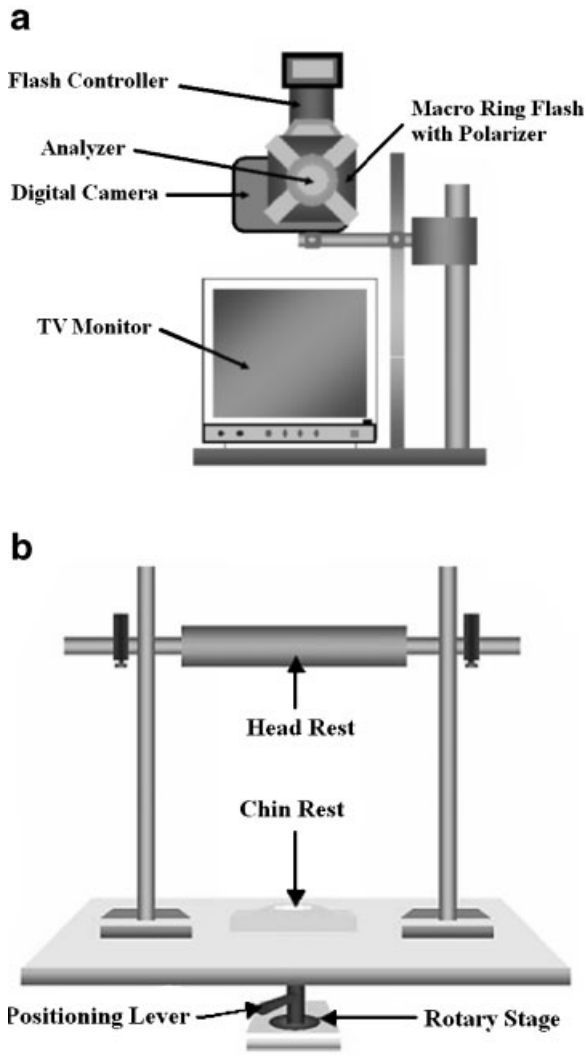

Fig. 1. **a**: Diagram of the cross-polarized diffuse reflectance imaging system and **b**: the head positioning device used to standardize images obtained from each subject.

PWS Subjects

Subjects with facial PWS lesions (n = 17) undergoing laser therapy at the Beckman Laser Institute and Medical Clinic (BLI), were recruited for this study. *Of the 17 subjects, 9 had not previously received laser therapy, and 8 subjects had previously received laser therapy prior to their inclusion in the study. Subjects studied had Fitzpatrick type II-IV.* All patients received one laser treatment using a PDL (C-beam, $\lambda = 585$ nm, 0.45 ms pulse duration, 7 mm spot size, Candela Corp., Wayland, MA). Cross-polarized skin color images were taken from each subject before and after 8 weeks of laser therapy.

Erythema Index (EI) Image Analysis

Calculation of an EI image was determined with a Dermaspectrometer (Cortex Technology, Denmark), in which two diodes emitting within a narrow range centered at 568 nm (green light) and 655 nm (red light) are used and the absorbance index at each band defined according to the theory of Dawson et al. [20]. The equation for calculating EI has a strong positive correlation with a high melanin concentration [21]. Takiwaki et al. [21] modified the equation by introducing a weighting factor to the absorption index in the red band to reduce the influence of epidermal melanin on erythema quantification as follows:

$$EI = 100 \times [\log_{10}(1/R_g) - 1.44 \times \log_{10}(1/R_r)] \quad (1)$$

where $R_{r,\,g} = S_{r,g}/W_{r,g}$ and the subscripts 'r' and 'g' indicate red and green, respectively. $R_{r,g}$ are the normalized red and green reflectance images of the sample under study, respectively. $S_{r,g}$ are the acquired red and green color images of the sample and $W_{r,g}$ are the average red and green values of a 99% diffuse reflectance standard (Model SRT-99-100, Labsphere, North Sutton, NH), respectively. In an EI image, a higher index value indicates a higher *degree of* erythema.

ΔEI Image Analysis

EI images provide absolute erythema indices. In most cases, PWS subjects require multiple treatments over a period of several months or years. Therefore, use of an EI image is susceptible to factors, such as instabilities in the imaging system and seasonal changes in epidermal melanin concentration. *Since PWS skin consists of a histologically normal epidermis* [22], *we do not anticipate that epidermal melanin content differs between normal and PWS skin*. To minimize the effect of such factors on image analysis, a ΔEI image was computed as follows:

$$\Delta EI = EI_{si} - EI_{sna} \quad (2)$$

where EI_{si} is the selected EI image, including PWS and normal skin and EI_{sna} is the average EI value of selected normal skin sites. Therefore, the ΔEI image emphasizes the ΔEI between PWS and normal skin. In the image analysis presented herein, *the* **Δ***EI value was used to measure the difference in the degree of erythema between PWS and normal skin.*

In the ΔEI image analysis, a concerted effort was made to select identical skin sites, which include PWS and normal skin, from ΔEI images of each subject before and after PWS laser therapy. For qualitative analysis, ΔEI values ranging from 40 to 0 were classified into 8 different ranges for moderate visualization of the ΔEI distribution. For quantitative analysis, percent erythema area (ΔEI_{area} (%)) from an ΔEI image (Eq. 2) was defined in Equation (3) and computed for five different ΔEI ranges of 40–31, 30–21, 20–11, 10–6, and 5–0, in which the ranges of 40–6 and 5–0 were classified as PWS and normal skin, respectively, based on analysis of previous PWS patients.

$$\Delta EI_{area}(\%) = (\Delta EI_s/\Delta EI_t) \times 100 \quad (3)$$

where ΔEI_s represents the number of pixels in the selected ΔEI range, and ΔEI_t, the total number of pixels in the selected ΔEI image.

To study PWS skin responses in terms of erythema area as a function of pretreatment ΔEI values, the percent change of ΔEI_{area} ($_{ratio}\Delta EI_{area}$ (%)) after laser therapy was computed for each ΔEI range using the following equation:

$$_{ratio}\Delta EI_{area}(\%) = [(_{after}\Delta EI_{area} - {}_{before}\Delta EI_{area})/{}_{before}\Delta EI_{area}] \times 100 \quad (4)$$

where $_{before}\Delta EI_{area}$ and $_{after}\Delta EI_{area}$ represent the ΔEI_{area} before and after laser therapy, respectively. In PWS, ΔEI range (40–6), negative and positive $_{ratio}\Delta EI_{area}$ represents a decrease and increase in the area of the PWS lesion, respectively. In normal skin, ΔEI range (5–0), positive and negative $_{ratio}\Delta EI_{area}$ represents an increase and decrease in the area of normal skin, respectively.

To study site-by-site PWS skin response to laser therapy, each ΔEI image before and after laser therapy was segmented into four regions and an average ΔEI value computed for each region. A total of 68 pairs of ΔEI values were computed from 17 ΔEI subject images and their relationship investigated using regression analysis.

RESULTS

Figure 2 shows representative cross-polarized color (top) and ΔEI (bottom) images before (left) and after (right) PWS laser therapy, for two subjects. The ΔEI image in Figure 2a shows that *the ΔEI values (region 1) were lower after laser therapy due to the fading of the PWS in response to PDL therapy*. In this example, the erythema spatial pattern generally remained unchanged. Region 2 in Figure 2a shows a substantial change in the erythema spatial pattern due to complete PWS blanching in some areas. *Therefore, ΔEI values approached those of normal skin in response to PDL therapy*. The average ΔEI values before and after PWS laser therapy in region 1 were 10.6 and 6.0, and in region 2 were 8.4 and 4.1, respectively. *The ΔEI images in* Figure 2b *also show considerable changes in the erythema spatial pattern due to the fading of PWS in different areas following PDL therapy*. Average ΔEI values before and after PWS laser therapy in the square were 3.1 and 4.9, and in the oval region were 6.7 and 2.8, respectively. We qualitatively analyzed ΔEI images of all 17 PWS subjects and observed similar findings to those described above.

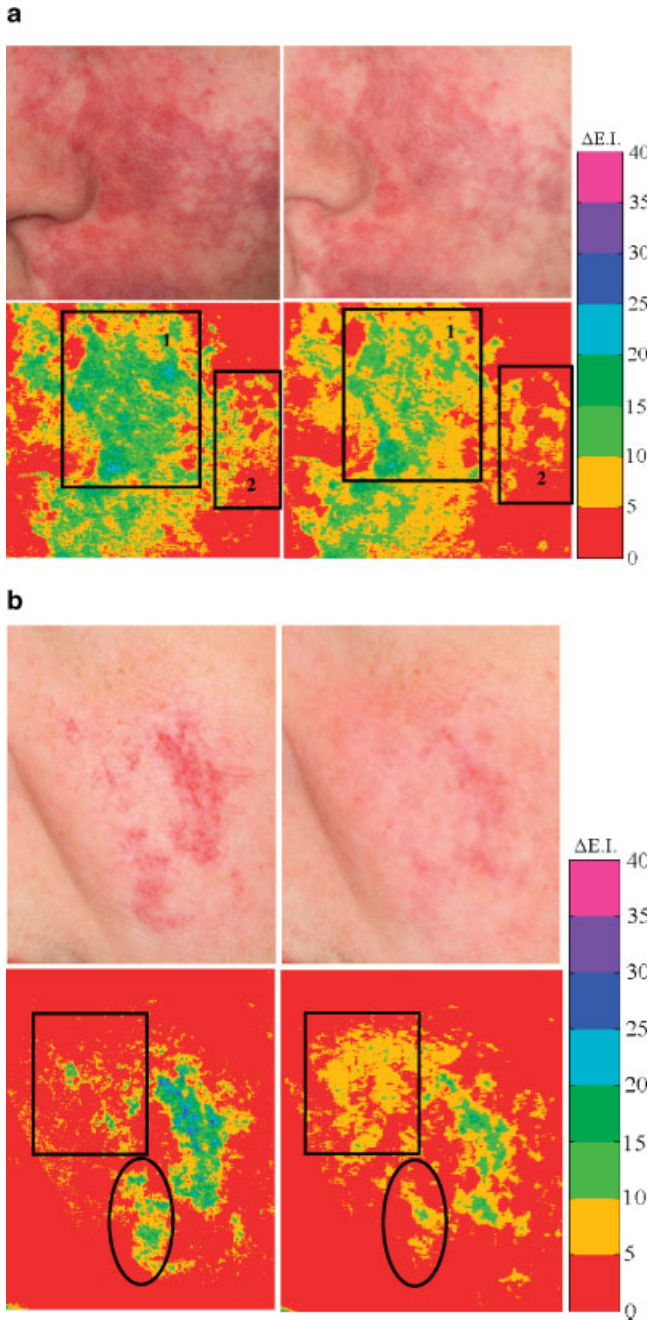

Fig. 2. Cross-polarized skin color images (**top**) and ΔEI images (**bottom**) before (**left**) and after (**right**) PWS laser therapy of two subjects (**a** and **b**). The ΔEI images were classified into eight ΔEI ranges. A higher ΔEI value in the colorbar indicates a higher degree of erythema. The ΔEI range of 5–0 was considered as normal skin and larger values as PWS skin.

Based on the qualitative analysis described above, Equation (3) was used to quantitatively determine the percent erythema area (ΔEI_{area} (%)) before and after PWS

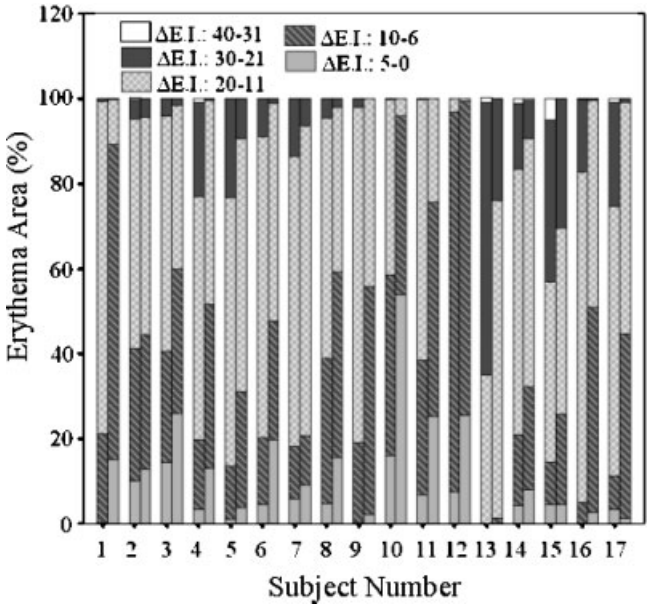

Fig. 3. The percent erythema area (ΔEI_{area} (%)) within each ΔEI range before (**left bar**) and after (**right bar**) laser PWS therapy. Total percent erythema area of PWS skin before and after laser therapy was the same (100%).

TABLE 1. Summary of Percent Change in ΔEI_{area} ($_{ratio}\Delta EI_{area}$ (%)) After One PWS Laser Treatment

	$_{ratio}\Delta EI_{area}$ (%)				
Patient #	ΔEI: 40-31	ΔEI: 30-21	ΔEI: 20-11	ΔEI: 10-6	ΔEI: 5-0
1	N/A	−90	−90	260	3680
2	−70	−10	−10	0	30
3	−100	−60	−30	30	80
4	−100	−100	−20	170	280
5	−100	−60	−10	120	260
6	N/A	−90	−30	80	320
7	N/A	−50	10	0	50
8	N/A	−60	−30	30	230
9	N/A	−100	−40	190	450
10	N/A	−100	−90	0	230
11	N/A	−100	−60	60	260
12	N/A	N/A	−80	−20	230
13	−100	−60	120	120	0
14	−50	−40	−10	40	90
15	−100	−20	0	120	0
16	−100	−100	−40	860	2800
17	−100	−100	−10	450	−60
Average	−91	−71	−24	147	525

laser therapy. The results are presented in Figure 3, in which total ΔEI_{area} (%) is 100% both before (left bar in each subject) and after (right bar in each subject) PWS laser therapy. For all subjects, ΔEI_{area} decreased in the ΔEI range of 40 through 21 after PWS laser therapy. However, ΔEI_{area} in the ΔEI range of 20 through 11 increased in 1 subject, decreased in 15 subjects, and did not change in 1 subject. ΔEI_{area} in the ΔEI range of 10 through 6 increased in 13 subjects, decreased in 1 subject, and did not change in 3 subjects. In the normal skin area (ΔEI: 5–0), ΔEI_{area} increased in 14 subjects, decreased in 1 subject, and did not change in 2 subjects. The average ΔEI_{area}s of all subjects before (after) PWS laser therapy were 1.1 (0.1)%, 15.2 (5.7)%, 55.9 (42.6)%, 22.9 (38)%, and 5.2 (14.1)% for the five ΔEI ranges of 40–31, 30–21, 20–11, 10–6, and 5–0, respectively. The ΔEI range of 20 through 11 represented the largest area of PWS skin, both before and after laser therapy.

We found that PWS skin response was dependent on pretreatment ΔEI values. For each subject, $_{ratio}\Delta EI_{area}$ (%) was summarized in Table 1. For PWS skin (ΔEI: 40–6), a $_{ratio}\Delta EI_{area}$ of −100% indicates complete PWS removal within the specified ΔEI range. The $_{ratio}\Delta EI_{area}$ for all subjects show a consistent pattern as a function of ΔEI values. Relatively high ΔEI values (40–11) resulted in a larger percent reduction in the area of PWS erythema. However, lower ΔEI values (10–6) resulted in a percent increase in the area of PWS erythema. The average $_{ratio}\Delta EI_{area}$ values across all subjects were −91, −71, −24, 147, and 525% in the ΔEI ranges of 40–31, 30–21, 20–11, 10–6, and 5–0, respectively. In PWS skin (ΔEI: 40–6), the average $_{ratio}\Delta EI_{area}$ decreased in the ΔEI range of 40 through 11 and then increased, *suggesting* in general that higher ΔEI values resulted in a better PWS blanching response to laser therapy. The extremely high $_{ratio}\Delta EI_{area}$ value (patients numbered 1 & 16) in Table 1 resulted from the extremely small ΔEI_{area} (close to zero) before PWS laser therapy (see Fig. 2). The $_{ratio}\Delta EI_{area}$ increased in normal skin area (ΔEI: 5–0).

The regression analysis (Fig. 4) suggested that PWS with higher pretreatment ΔEI values results in higher reduction in ΔEI values after PWS laser therapy, supporting the data shown in Table 1. The linear regression fitting ($\Delta EI_{after} = 0.782\,\Delta EI_{before} = 0.378$) of ΔEI values before and after PWS laser therapy indicated a strong positive linear correlation ($R = 0.87$).

DISCUSSION

Previous publications [14–16,19,23] have presented quantitative color assessments of PWS skin. One approach involves analysis of digitized analog images taken before and after PWS laser therapy [15,16]. A limitation of this approach is the lack of standardization of the imaging environment, which can lead to substantial errors in analysis of color changes and PWS lesion size [14,19]. A second approach is the use of reflectance photometry [23], which has limitations due to the fact that the acquired data is inherently a point measurement, and thus spatial information is not preserved. With this approach, a gradual decrease in EI was observed with successive treatments [23]. Advantages of our approach include standardization

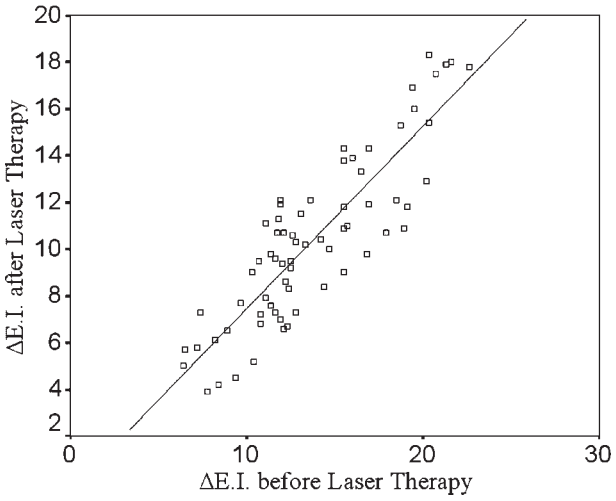

Fig. 4. Linear regression analysis of site-by-site ΔEI values before and after laser therapy, suggesting a strong positive correlation (R = 0.87). This suggests that PWS skin response depends on pretreatment ΔEI values.

of the imaging environment and inherent flexibility of image analysis, either on a pixel by pixel basis (Fig. 2) or average EI values over an area (Figs. 3 and 4).

PWS response to laser therapy was dependent on pretreatment ΔEI values (Fig. 4). Relatively high ΔEI values (40–11) resulted in greater percent reductions in erythema area (Table 1). ΔEI values after laser therapy have a strong positive linear correlation with the pretreatment ΔEI values (Fig. 4). Similar results were noted by Koster et al. [3] in which higher color differences between PWS and normal skin required more treatments to completely blanch the PWS in response to laser therapy.

PWS erythema results from the presence of multiple dilated dermal blood vessels. Therefore, changes in erythema can be attributed to vessel removal and shrinkage of perivascular tissue in response to laser therapy. PWS skin has a complex vascular structure and is composed of clusters of vessels [24]. However, the ΔEI value is an indirect measure of PWS characteristics, such as number of vessels, and their depth and diameter. Therefore, our results must be interpreted with some caution as we attempt to relate PWS erythema to individual blood vessel lesion geometry.

It is well known that treatment response after laser therapy varies with PWS skin color, vessel diameter, and depth [7,9,10,25,26]. Based on the results of the previous studies, we assume that a higher ΔEI represents superficial or large blood vessel clusters while a lower ΔEI represents deeper or smaller vessel clusters. The reduction in erythema area with higher ΔEI values (ΔEI: 40–11) following laser therapy may indicate that the superficial and/or large blood vessels are removed, revealing deeper vessels or clusters of smaller vessels. An increase in the erythema area with relatively lower ΔEI values (ΔEI: 10–6) may be due to incomplete elimination of blood vessels, reformation of blood vessels, or removal of more superficial blood vessels with subsequent visualization of deeper blood vessels. The increase in the area of normal skin (ΔEI: 5–0) might indicate that part of the PWS network was successfully treated.

In this study, to maximize our ability to directly compare images acquired at different imaging sessions, we controlled camera settings and view angle. We did not control ambient temperature or take into account the physical conditioning of each subject. To address the former issue, we envision a scenario in which the subject first stays in a room with controlled temperature for a period of 30 minutes to achieve equilibrium conditions. Future studies will incorporate such a change in protocol.

In conclusion, PWS skin response to laser therapy was dependent on pretreatment ΔEI values, suggesting the feasibility of using ΔEI as a predictive factor of PWS response to laser therapy. The classified ΔEI image can be utilized to monitor the subject- and site-dependent PWS skin responses to laser therapy. The results of the regression analysis (Fig. 4) may be used to predict treatment efficacy. For example, if the pretreatment ΔEI value is 30, then the expected value after therapy would be 23. If the outcome is less than expected, then the clinician would be encouraged to try an alternative set of laser treatment parameters.

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