Analysis of portwine stain disfigurement and pulsed dye laser treatment results
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Chapter 6

Prediction of portwine stain clearance and required number of flashlamp pumped pulsed dye laser treatments

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Abstract

Portwine stain response to flashlamp pumped pulsed dye laser treatment is variable and unpredictable. Our aim was to develop a model to predict treatment outcome and the required number of treatments. We hypothesized that portwine stain clearance decreases exponentially with the number of treatments, as a consequence of the exponential decrease of laser light fluence in human skin.

Of 70 patients with a portwine stain in the head/neck area, the color difference between normal skin and portwine stain was measured with a chromameter, prior to, and at several stages during flashlamp pumped pulsed dye laser treatment. Through the obtained values of each of the four color parameters $\Delta L^*$, $\Delta a^*$, $\Delta b^*$ and $\Delta E$, mono-exponentially decreasing functions were fitted.

All color parameters showed similarly decreasing exponential functions, with a mean $R^2$ of 0.6, indicating a reliable fit-quality.

Our model suggests that individual prediction of treatment outcome and the required number of treatments is possible in an early stage of flashlamp pumped pulsed dye laser treatment of portwine stains, in theory already after one single laser treatment. This may enable realistic treatment planning, benefiting patient, physician, and health insurance company.
Introduction

Portwine stains are vascular birthmarks caused by ectatic dermal blood vessels. Portwine stains are amenable to treatment with the flashlamp pumped pulsed dye laser, but response is variable and the number of treatments necessary to achieve the best possible clearance unpredictable. Multiple studies have tried to identify prognostic portwine stain parameters, but the results of these studies have not been ultimately satisfying. The methods used to relate treatment response to portwine stain parameters are either based on invasive techniques, using histological evaluation of skin biopsies, or yield only rather rough estimations of the treatment outcome to be expected. Therefore, individual treatment planning based on non-invasively established prognostic factors is currently not possible. Our aim was to develop a model to predict treatment outcome and the required number of treatments in an early stage of flashlamp pumped pulsed dye laser treatment of a portwine stain.

Although the concept underlying flashlamp pumped pulsed dye laser treatment, selective photothermolysis, is well-known, the mechanism of portwine stain clearance in response to multiple flashlamp pumped pulsed dye laser treatments is incompletely understood. However, it is generally assumed that the flashlamp pumped pulsed dye laser destroys the ectatic vessels layer by layer. With the first laser treatment the uppermost layer of portwine stain vessels is destroyed. Subsequent wound healing then replaces the ectatic vessels by normal size vessels. In the next treatment less laser light will be absorbed in this layer, allowing the laser light to penetrate deeper into the skin and destroy a deeper layer of vessels. However, laser light fluence decreases exponentially with skin depth. We assume that consequently the number of vessels destroyed in each consecutive layer decreases exponentially, resulting in the hypothesis that portwine stain clearance decreases exponentially with the number of treatments. Model calculations of skin color after flashlamp pumped pulsed dye laser treatment indeed suggest this exponential behaviour.
interestingly, a mono-exponentially decreasing clearance would allow prediction of treatment outcome and the required number of treatments. In theory, this would already be possible after only one treatment or test patch. We investigated whether portwine stain clearance as a result of flashlamp pumped pulsed dye laser therapy can be represented by a mono-exponential function of the number of treatments of the portwine stain. We used available color measurements taken before and during treatment.\textsuperscript{15}

**Materials and methods**

70 patients (24 male, 46 female, age at start of treatment \(0\) to 31 yr, mean 13.3 yr, sd 8.3 yr) with previously untreated portwine stains in the head-neck region were treated during a period of three years with the Candela SPTL flashlamp pumped pulsed dye laser (wavelength 585 nm, pulse duration 0.45 ms, spot size 5 mm, repetition rate 0.3 Hz).

Color measurements were taken with a Minolta chromameter, type CR-300. Colors were represented by \(L^*a^*b^*\) coordinates, where \(L^*\) denotes lightness, representing the object's reflectance relative to a 100 percent ideal 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); \(b^*\) denotes values from blue to yellow (negative values indicate blue and positive values yellow).\textsuperscript{16}

Color measurements were taken prior to treatment and at several stages during treatment. Both portwine stain and contralateral healthy skin were measured and the color difference \(\Delta E\) between these two was calculated according to

\[
\Delta E = \sqrt{(\Delta L^*)^2 + (\Delta a^*)^2 + (\Delta b^*)^2} \tag{1}
\]

where \(\Delta L^*, \Delta a^*\) and \(\Delta b^*\) represent the differences in the measured \(L^*, a^*\) and \(b^*\) values between normal skin and portwine stain.
For each patient these differences ($\Delta L^*$, $\Delta a^*$, $\Delta b^*$ and $\Delta E$) were plotted as a function of the number of treatments of the entire lesion. Then, for each of the differences a mono-exponential function was fitted through these data, using a least-squares procedure. This mono-exponential function is defined as

$$\Delta X(n) = \Delta X(0) \cdot \left(e^{-K_{\Delta X}}\right)^n$$

with $\Delta X = \Delta L^*$, $\Delta a^*$, $\Delta b^*$ or $\Delta E$. (2)

In this equation $\Delta X(n)$ is the fitted value for $\Delta L^*$, $\Delta a^*$, $\Delta b^*$ or $\Delta E$ after $n$ treatments, $\Delta X(0)$ is the fitted value for $\Delta L^*$, $\Delta a^*$, $\Delta b^*$ or $\Delta E$ before treatment, and $K_{\Delta L^*}$, $K_{\Delta a^*}$, $K_{\Delta b^*}$ and $K_{\Delta E}$ respectively represent the rate of decay of the fitted curve. A characteristic property of a mono-exponentially decaying function is that the percentage reduction with each step is the same. From the rates of decay ($K_{\Delta L^*}$, $K_{\Delta a^*}$, $K_{\Delta b^*}$, and $K_{\Delta E}$), the percentage reduction of $\Delta L^*$, $\Delta a^*$, $\Delta b^*$ and $\Delta E$ with each treatment can therefore be calculated as

percentage reduction in $\Delta X$ per treatment $= 100 \cdot \left(1 - e^{-K_{\Delta X}}\right)$. (3)

For $K_{\Delta X} << 1$, which is always the case here (see Fig. 2), Eq. (3) can be simplified to

percentage reduction in $\Delta X$ per treatment $= 100 \cdot K_{\Delta X}$ %. (4)

Eq. (4) shows that with each treatment, parameter $\Delta X$ is reduced by the same percentage (see Appendix).
Results

On average, 6 color measurements minimum 3, maximum 12, were available per patient measured during a period of three years, covering an average of 6 treatments of the entire porthole start minimum 2, maximum 13.

Table 1 summarizes the least squares fits results for $A^*, A_{a}^*$, $A_{b}^*$ and $A^*$ is a function of the number of treatments, averaged over all 70 patients. With an average $R^2$ of 0.99, the fit almost supports the choice of a monoexponential function.

![Table 1](image)

Table 1. Results of the least-squares fits for $A^*, A_{a}^*$, $A_{b}^*$ and $A^*$ as a function of treatment number, averaged over all 70 patients.

<table>
<thead>
<tr>
<th></th>
<th>mean</th>
<th>sd</th>
<th>95 percent confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A^*$</td>
<td>10.2</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>$K_{A^*}$</td>
<td>0.6</td>
<td>0.19</td>
<td>0.12 ± 0.21</td>
</tr>
<tr>
<td>$A_{a}^*$</td>
<td>0.4</td>
<td>0.0</td>
<td>0.0 ± 0.0</td>
</tr>
<tr>
<td>$K_{A_{a}^*}$</td>
<td>0.3</td>
<td>0.0</td>
<td>0.0 ± 0.0</td>
</tr>
<tr>
<td>$A_{b}^*$</td>
<td>0.3</td>
<td>0.15</td>
<td>0.10 ± 0.17</td>
</tr>
<tr>
<td>$K_{A_{b}^*}$</td>
<td>4.0</td>
<td>2.3</td>
<td>3.4 ± 4.6</td>
</tr>
<tr>
<td>$A_{r}^*$</td>
<td>0.78</td>
<td>0.23</td>
<td>0.03 ± 0.14</td>
</tr>
<tr>
<td>$K_{A_{r}^*}$</td>
<td>14.5</td>
<td>4.8</td>
<td>3.4 ± 15.8</td>
</tr>
<tr>
<td>$K_{A}$</td>
<td>0.12</td>
<td>0.0</td>
<td>0.10 ± 0.14</td>
</tr>
</tbody>
</table>

According to our model, in these 70 patients, mean $A^*(0) = 10.2$ means that the fitted $A^*$ starts at 10.2 and with $K_{A^*} = 0.16$, the fitted curve predicts a reduction in $A^*$ of 15 percent with each treatment. Likewise, the fitted $A_{r}^*(0)$ for all 70 patients is 0.41, and the reduction of $A_{r}^*$ with each treatment is 13 percent. For $A_{b}^*$ these values are 4.0 and 8 percent respectively. $A^*$ starts at 14.5 and is reduced by 12 percent with each treatment.

The rate of decay, $K_{A_{r}^*}$ is not significantly different for $A^*, A_{a}^*, A_{b}^*$ and $A^*$ respectively, as can be concluded from the confidence intervals in Table 1.
Fig. 1 shows the fitted exponential curves averaged over the seventy patients.

Fig. 1: Fitted exponential curves averaged over the seventy patients. Dashed lines indicate extrapolations of these curves beyond the number of treatments accomplished.
The large confidence intervals seen in Table 1 are due to a large variation in the rate of decay ($K_{AX}$) between patients. This is demonstrated for the perceived color difference ($\Delta E$) between normal skin and portwine stain in Fig. 2, which shows the number of patients versus $K_{AE}$.

![Histogram showing number of patients versus $K_{AE}$](image)

**Fig. 2:** Number of patients (total=70) versus $K_{AE}$. A small $K_{AE}$ indicates a small reduction of $\Delta E$ with each treatment, a large $K_{AE}$ a large reduction. For example, a $K_{AE}$ of 0.05 indicates a $\Delta E$-reduction of 5 percent with each treatment, a $K_{AE}$ of 0.3 indicates a reduction in $\Delta E$ of 30 percent.

Having established a patient's $K_{AE}$, i.e. the rate of decay of the monoeexponential fit of $\Delta E$, the number of treatments ($N_{%C}$) necessary to achieve a desired percentage of clearance ($%C$) can be calculated by

$$N_{%C} = \frac{1}{K_{AE}} \cdot \ln \left( \frac{100}{100 - %C} \right)$$  \hspace{1cm} (5)
Discussion

In our 70 patients, analysis of the reduction in color difference (ΔE) between normal skin and portwine stain in response to flashlamp pumped pulsed dye laser treatment, shows an average rate of decrease (KΔE) of 0.12, meaning that ΔE is reduced by 12 percent with each treatment. Calculation of the number of treatments necessary to achieve a desired percentage of clearance (Eq. 5), reveals that on average 5-6 treatments of the entire portwine stain are required to achieve 50 percent clearance. Extrapolating these results, a number of almost 20 treatments is predicted to achieve 90 percent clearance. These predictions are supported by clinical results of others.\textsuperscript{19,21}

We could not detect differences in treatment response between younger and older patients, nor between males and females.

The rate at which ΔE decreases in response to flashlamp pumped pulsed dye laser treatment (KΔE) was found to be uncorrelated with the initial color difference between portwine stain and normal skin (ρ = -0.002), meaning that light and dark portwine stains are equally responsive to flashlamp pumped pulsed dye laser treatment.

The rates of decay of the fitted curves for ΔL*, Δa*, Δb* and ΔE (i.e. KΔL*, KΔa*, KΔb*, and KΔE) are not significantly different from each other, implying that flashlamp pumped pulsed dye laser treatment influences each color parameter to a similar extent.

Large variations are found in clearance rates (KΔE; see Fig. 2), which is in accordance with the clinical experience of most authors. This means that the average model depicted in Fig. 1 is of limited value for individual patients. But having demonstrated that portwine stain clearance can be reliably represented by an exponentially decreasing function of the number of treatments, individual curves based on two or three color measurements can be fitted. Troilms and Ljunngren\textsuperscript{21} used a similar method to assess treatment response. Haedersdal et al. emphasize the importance of being able to establish when further treatment is without additional benefit to the patient.\textsuperscript{22}
Our model of portwine stain clearance as a mono-exponential function of the number of flashlamp pumped pulsed dye laser treatments, allows individual prediction of the best possible portwine stain clearance and the required number of treatments. Theoretically, this is already possible after the first treatment or test patch, but predictions become more accurate after two or three treatments. With this model we have developed a tool that enables realistic treatment planning, benefiting patient, physician and health insurance company.

Fig. 3 shows an example of measured values (in this case the color difference, $\Delta E$, calculated from the measured $L^*$, $a^*$ and $b^*$ values), the corresponding fitted curve and photographs of the patient before and after several numbers of treatment of her entire lesion.

![Graph showing measured values of $\Delta E$ against the number of treatments.](image)

**Fig. 3a:** Measured values of $\Delta E$ with the fitted mono-exponential function for one of the 70 patients. The fitted $\Delta E(0) = 20.9$, $K_{AE} = 0.24$, and $R^2 = 0.91$. 

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Fig. 3b: (see also next page) Photographs of the patient from Fig. 3a.

Panel A: before treatment,
Panel B: after 1 treatment of the entire lesion,
Fig. 3b: (continued) Photographs of the patient from Fig. 3a.
Panel C: after 2 treatments of the entire lesion,
Panel D: after 4 treatments of the entire lesion.
References


Appendix: Derivation of Equation (4)

Starting with Eq. (2)

$$\Delta X(m) = \Delta X(0) \cdot \left(e^{-K_{\Delta X}}\right)^m$$  \hspace{0.5cm} (2)

Substitution on \((n+1)\) and \(n\) for \(m\) in Eq. (2), it can easily be shown that

$$\frac{\Delta X(n+1)}{\Delta X(n)} = e^{-K_{\Delta X}}.$$ 

This means that the relative reduction in \(\Delta X\) per treatment is given by

$$\frac{\Delta X(n) - \Delta X(n+1)}{\Delta X(n)} = 1 - \frac{\Delta X(n+1)}{\Delta X(n)} = 1 - e^{-K_{\Delta X}}.$$ 

For \(K_{\Delta X} \ll 1\), which in our results was always the case, a Taylor series expansion of the exponent, and using the first two terms only, gives

$$1 - e^{-K_{\Delta X}} = K_{\Delta X},$$

meaning that the relative reduction per treatment is given by \(K_{\Delta X}\), or, expressed as a percentage reduction, by \(100 \cdot K_{\Delta X} \%\).