Improvement of disfiguring skin conditions by laser therapy
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DOUBLE PASS 595 NM PULSED DYE LASER AT A 6 MINUTE INTERVAL FOR THE TREATMENT OF PORT-WINE STAINS IS NOT MORE EFFECTIVE THAN SINGLE PASS

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*in alphabetical order; both authors contributed equally to this paper

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ABSTRACT

Background: Pulsed dye laser (PDL) is the first choice for treatment of port-wine stains (PWS). However, outcome is highly variable and only a few patients achieve complete clearance. The objective of the study was to compare efficacy and safety of single pass PDL with double pass PDL at a 6 minute interval.

Methods: We conducted a randomized within-patient controlled study on PWS resistant to multiple single pass PDL treatments. In each patient two similar PWS areas were randomly allocated to PDL treatment (595 nm, 7 mm spot size, 1.5 ms pulse duration) using, as a control treatment, a single pass (12 J/cm²) or, as a new treatment, a double pass PDL (11 J/cm², second pass 6 minutes after the first pass). Both test areas were treated two times, 8 weeks apart. PWS clearance was assessed by two blinded dermatologists, and by color measurement (L*a*b) using reflectance spectroscopy, at 3 months follow-up.

Results: Sixteen out of 17 included patients completed follow-up. The mean number of treatments before inclusion was 15. Overall color assessed by spectrophotometer showed no improvement for either single or double pass PDL. Blinded Physician Global Assessment and Patient Global Assessment showed a high variability in outcome, with mostly only moderate improvement of the PWS for either single pass or double pass PDL. Furthermore, there was no significant difference in any of the outcomes between single pass and double pass PDL.

Conclusion: At the chosen settings and after two treatment sessions, double pass PDL at a 6 minute interval does not result in improved clearance of PWS as compared to single pass treatment.
INTRODUCTION

Port-wine stains (PWS) are benign congenital vascular malformations characterized by ectatic blood vessels situated mainly in the superficial dermis. They afflict 0.3% of all newborns. A negative effect of PWS on the quality of life has been demonstrated in several studies. The pulsed dye laser (PDL) is the standard of care for the treatment of PWS. The goal of this laser treatment is to cause irreversible thermal damage to vessels while sparing adjacent tissues. In recent years, the 595 nm PDL has become the laser of choice for the treatment of PWS. However, multiple treatments are required and only a minority of patients achieves total clearance of the PWS.

Reasons for poor response of PWS to laser treatment may be subcritical fluence rates at the target vessels, due to the depth and/or the size of these vessels, or shadow effect of other than the target vessels. The depth of PWS vessels varies from 100 to 1000 µm, and the diameter of PWS vessels ranges from 10 µm to 300 µm. Vessels smaller than approximately 20 µm will pose a problem to any type of laser as the heat generated by absorption of laser light is insufficient to cause vessel destruction. Furthermore, deeper situated large diameter vessels will only be partially damaged by laser therapy and recover soon after treatment.

One way to increase vascular damage is the use of multiple pass techniques. Verkruysse et al. showed a PWS model in which the multiple-pulse laser irradiation favors damage to PWS blood vessels. They therefore suggested multiple-pulse dye laser as an alternative therapy for PWS that fail to respond to single-pulse dye laser treatment. In one such technique, referred to as pulse stacking, 2 to 4 sequential pulses with relatively short pulse intervals are applied to every treated spot. Pulse stacking has been shown to be safe and effective in the treatment of superficial telangiectasia. In the treatment of hypertrophic PWS a second pass has been reported to be safe and effective in four patients. However, Lorenz et al., using exactly the same technique and settings in 33 patients with PWS, could not confirm the benefit of a second pass as compared to conventional single pass treatment.

Based on histological assessment of vascular damage of non-PWS skin, Tanghetti et al. suggested that multiple pass PDL treatment may be beneficial but stressed the relevance of the interval between pulses. They found that a double pass resulted in a monotonic increase in the depth of vascular injury when increasing the interval between passes up to 30 minutes. Koster et al. found that overlapping pulses on normal skin enhances the depth of vascular damage by approximately 30%. In pulse stacking this interval is approximately 1 second. A longer interval may be more effective as thrombus formation is a dynamic process evolving for an extended period after the laser pulse. In laser-induced thrombus formation in isolated hamster dorsal skin fold venules, the maximum size of the thrombus is reached at a 6 minute interval. The absorption of coagulated blood is higher than non-coagulated blood. Consequently, a second laser pulse after 6 minutes can generate more heat than the first one. Thus, it can accumulate damage within the partially blocked vessels attempting to totally occlude these vessels. The clinical effect of a second laser pulse after 6 minutes on the improvement of PWS has not been evaluated yet.
The purpose of this study was to assess the efficacy and safety of double pass PDL in resistant PWS at a 6 minute interval as compared to single pass PDL.

**METHODS**

**Patients**

Patients with a PWS located in the face or trunk, who attended the laser department of the Netherlands Institute of Pigment Disorders (SNIP) at the Academic Medical Center Amsterdam (AMC), were recruited between March and December 2007. We included all patients above 17 years of age, with at least 3 previous PDL treatments of their PWS with insufficient improvement, and a PWS large enough to mark two comparable areas of 2x2 cm with at least 0.5 cm in between. The location of the two areas was accurately documented on transparent sheets and on photographs. The PWS were classified according to color (pink, red, purple, and dark purple). Subjects were excluded if the PWS was hypertrophic or dark purple to help create a homogeneous group of PWS patients. For the power analysis, we estimated that double pass PDL will lead to 15% more PWS clearance after 2 treatments, when compared to single pass PDL. Previous clinical studies on double pass PDL treatment were not controlled, and therefore no reliable clearance outcomes were available. From a clinical point of view, we considered a difference of 15% to be relevant. A sample size of 16 patients would have a power of 80% with an alpha of 0.05 to detect a difference in PWS clearance of 15%. This study was given approval by the Medical Ethical board of the AMC and written informed consent was obtained from all patients.

**Intervention**

Two similar colored areas of the PWS measuring 2x2 cm were randomly allocated to either a single pass or two subsequent passes with the PDL (6 minute interval). The randomization procedure involved sealed envelopes in which the allocation was indicated. The sealed envelopes were numbered from 1-16. Envelopes were opened in ascending order. The random allocation sequence was created using a digital randomization program (Graphpad Software Inc.). For the treatment we used a 595 nm PDL (V-beam, Candela Corporation Inc., Wayland, MA) with a 7 mm spot size, 1.5 ms pulse duration, 30 ms spurt duration of dynamic cooling and 20 ms spurt-pulse interval, with 10% overlapping of spots. The radiant exposure per pulse was 12 J/cm² for single pass PDL and 11 J/cm² for double pass. The settings for single pass PDL are regularly used for the treatment of PWS at our institute and have been used previously in several trials with PWS. The optimal radiant exposure for double pass treatment is unclear. To minimize the risk of side-effects such as scarring, we decided to lower the energy in the double pass test areas. Furthermore, each patient waited in the same temperature-controlled room at 21°C for 30 minutes prior to treatment to reduce error from sympathetic stimulation and vasodilatation of the capillaries. Eight weeks (± 2 weeks) after the first treatment both selected regions were again treated with the same laser settings. During the study, patients were advised to avoid sun exposure and were encouraged to use topical sun protection (SPF> 30).
Measurements

Three months after the second treatment, the clearance of the PWS was assessed using both clinical assessment and color measurement. The clinical assessment of the treatment response was performed by 2 blinded dermatologists using the Physician Global Assessment (PhGA). They evaluated digital photographs taken before treatment (baseline) and at 3 months after the second treatment. All photographs were taken under standardized conditions for background, position of patient, light source and exposure as applied in other studies.\textsuperscript{25,26} All photographs were inserted into a PowerPoint file with standardized conditions for background and position. The blinded dermatologists assessed improvement using a visual analogue scale (VAS) ranging from 0 to 10 (0 = worsening or no improvement at all, 10 = complete clearance).\textsuperscript{8} Patients were also asked to evaluate the improvement of their PWS by using the Patient Global Assessment (PGA). They were asked to score the improvement on a scale of 1-4 (1 = poor, 2 = moderate, 3 = good, 4 = very good).

The color measurement was performed with a reflectance spectrophotometer (Microflash 200 d, Datacolor International, Lawrenceville, USA) before and 3 months after the second treatment. This instrument determines color by measuring the intensity of reflected light of particular wavelengths. Previously, color measurement has been found to be an objective, useful and non-invasive technique.\textsuperscript{6,27} The results are expressed in terms of Commission International d’Eclairage (CIE) Lab system, in which any color can be described by three values: L*, the lightness; a*, the amount of green or red; and b*, the amount of yellow or blue. We calculated the mean values of three measurements obtained from the darkest area of the PWS test regions and assessed the values from surrounding normal skin to correct for spontaneous variation in chromophores not related to laser treatment (e.g. pigmentation and spontaneous change in dermal blood flow). ΔE* is another outcome measure from the reflectance spectrophotometer and indicates the difference in overall color between PWS and normal skin by integrating the values of L*, a* and b* of both normal and PWS skin. Δa* indicates the difference in amount of redness between PWS and normal skin. At baseline, at 8 weeks and at 16 weeks, the adverse effects, including hypopigmentation, hyperpigmentation and scarring, were recorded by the investigators to ensure the safety of the patients.

Data analysis

For all data the means, standard deviations, and paired Wilcoxon signed-rank test were calculated in patients who complied with the protocol, using Statistical Package for the Social Sciences 16.0 (SPSS, Chicago, IL). For the clinical assessment, the mean scores of the two blinded investigators were used.

RESULTS

From the 23 consecutive patients who met the inclusion criteria, 6 patients declined the offer to participate. Seventeen patients (11 female; 6 male) were included between March 2007 and December 2007. One patient was unable to attend his second
treatment due to personal reasons not related to the treatment, and was excluded from analysis. The second treatment was performed after a mean of 9 weeks. The color of the PWS was purple in 13 patients, red in 3 patients and pink in 1 patient. The mean age was 39.5 years and the Fitzpatrick skin type was II (n=9) or III (n=8). The mean number of treatments prior to this study was 15.4 ± 11.6. Patients characteristics are all summarized in Table 1.

Blinded dermatologists judged that double pass resulted in better clearance in 3 patients while single pass was judged to be better in 7 other patients. In the remaining 6 patients no treatment was judged better than the other. In one patient of these 6 patients, the dermatologists judged that the results after treatment for both test areas were worse than pre-treatment (patient 6 in Figure 1, Physician Global Assessment).

The Patient Global Assessment (PGA) indicates that a majority of the patients assessed the outcome as poor or moderate (9 out of 16), while one patient rated the outcome of the double pass PDL better than the single pass. For both the PGA and PhGA there was an overall minor improvement of the PWS in both treated spots. However, there was no significant difference between single and double pass treatment.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>PWS Site</th>
<th>PWS Color</th>
<th>Number of earlier treatments</th>
<th>Skin type</th>
<th>Weeks to 2nd treatment</th>
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<tr>
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</table>

Mean ± SD 39.5 ± 13.6 15.4 ± 11.6 9

* = patient excluded from analysis.
Concerning the objective color measurements using a spectrophotometer, one patient could not be evaluated due to technical reasons. For this patient we only performed the clinical assessments (PGA and PhGA). For the remaining 15 patients we found a significant improvement of $\Delta a^*$ (difference in the amount of redness between PWS and normal skin) for the single pass but not for the double pass treatment ($p=0.01$ respectively $p=0.14$; Wilcoxon signed-ranks test). No significant change was found for $\Delta E^*$ (difference in overall color between PWS and normal skin) for both the single pass ($p=0.26$) and the double pass ($p=0.36$) PDL nor was there a difference in results between both modalities.

Side effects at 3 months follow-up were noticed in 5 patients. Two patients developed hypopigmentation at both the single and the double pass site. Three patients developed hyperpigmentation at both sites. One patient with hyperpigmentation at both sites also developed a slightly atrophic scar on the double pass site. This scar was still present at one year follow-up. Hyperpigmentation and hypopigmentation resolved spontaneously during follow-up. Side effects according to the patient were assessed by telephone one week after treatment. These side effects included temporary edema, crusts and oozing, and were similar for the test areas with single pass and the test areas with double pass in 11 patients. Side effects were more severe in the test area with double pass in 4 patients. There was no patient reporting more severe side effects for the single pass test area.

Furthermore, in this study it appeared that skin type, gender or number of treatments prior to this research did not affect the outcome.

**DISCUSSION**

We demonstrate that double pass PDL treatment at a 6 minute interval does not result in improved clearance compared to single pass treatment in PWS. This is the first randomized controlled trial assessing the effect of a second pass in PDL-treatment of PWS. Other,
non-controlled studies have been performed in the past with various outcomes. In the treatment of hypertrophic PWS, Bencini et al. reported a second pass with a flashlamp pumped PDL to be safe and well tolerated in four patients (first pass with a 590-600 nm FLPP dye laser 5 or 7 mm spot size, at 7.5-9.0 J/cm² fluence, 1.5 ms pulse duration, and second pass with a 585 nm FLPP dye laser 7 mm spot size, at 5.5-7.5 J/cm² fluence, 0.45 ms pulse duration). Lorenz et al. on the other hand, did not see any improvement in a study of 33 patients, using exactly the same multilayer technique. McGill et al. investigated the treatment of resistant PWS and found that the PWS of 5 out of 16 patients improved by double pass PDL, and 3 out of 16 by single pass PDL. However, objective color measurements showed no difference in color response.

Several limitations to our study need to be addressed. In the present study we used fixed settings for spot size, dynamic cooling, pulse duration, and radiant exposure. Choosing settings individually for each patient and each PWS may result in better outcomes. Possibly, in other conditions, or at a different inter pass interval, a double pass may be more effective. Furthermore, the small number of participants needs to be mentioned. While the sample size seems small to draw firm conclusions, there was not even a trend that favored the double pass PDL in any of the outcome measures. Another limitation is the highly selected population that comprised patients with non-hypertrophic resistant PWS who already had had many laser treatments before. Perhaps, hypertrophic PWS may benefit from a double pass while non-hypertrophic do not.

The interval of 6 minutes between passes was selected as a result of a previous study showing that the laser induced thrombus reaches its maximum size after 6 minutes. The interval between passes may be crucial in determining the vascular response. In the treatment of teleangiectasia, pulse stacking with 2 to 4 consecutive pulses (with a 595 nm pulsed dye laser 10mm spot size, at 7.5 J/cm² fluence, 10 ms pulse duration and 30-20 cooling device setting) was reported to increase efficacy. In the treatment of PWS there are no data available on the effect of pulse stacking. Tanghetti et al. found a monotonic increase in depth of vascular injury for intervals between pulses up to 30 minutes (with a 595 nm pulsed dye laser 7mm spot size, at 2-7 J/cm² fluence, 0.5 ms pulse duration). According to these data it is unlikely that a shorter interval between passes would result in a better outcome. However, observations by Tanghetti et al. were made in normal skin, which may show a different laser tissue interaction than PWS skin. McGill et al. found that some of the PWS improved by double pass PDL and some by single pass PDL (with a 585 nm pulsed dye laser 7mm spot size, at 7 J/cm² fluence, 0.45 ms pulse duration). They were using a 30 second interval between passes. Results from a recent retrospective study suggested that a second pass after 20 to 30 minutes with PDL (595 nm 7mm spot size, 9.5-15 J/cm² fluence, or 10mm spot size, 8-10 J/cm² fluence, 0.45-3.0 ms pulse duration and 30-20 or 40-20 cooling device setting) can further lighten some PWS, which are resistant to conventional single pass treatment. Conclusions were that only 5 out of 26 patients had significant lightening of the PWS after a minimum of three double-pass PDL treatments.
These studies all show variable outcomes. None of the studies used a control group. In some of these studies an extra benefit of a second pass is described, although most PWS show only minor improvement using different intervals between passes. Also, the optimal interval between passes remains unclear. Response to treatment is a multifactorial phenomenon, with capillary depth, capillary diameter, capillary flow rates, and epidermal melanin concentration all interacting to influence (non-)response to treatment. Consequently, prediction of the optimal treatment parameters is difficult. Variation of wavelength and/or pulse duration has been proposed to further improve resistant PWS. The comparison of PDL treatment at 585 nm versus 595 nm and 1.5 ms versus 0.45 ms provided inconsistent results which may indicate that settings have to be chosen individually. There are several theoretical reasons to explain the lack of efficacy of a second pass. Although a thermal coagulum can generate more heat by absorbing light, this coagulum may also cause optical shielding to underlying vessels. Moreover, extravasation of hemoglobin may also cause optical shielding. Secondly, the absence of hemoglobin in thrombocyte aggregates may result in insufficient absorption of light to cause photocoagulation; also, the blood flow in the remaining lumen may be too fast to allow formation of a permanent thermal coagulum.

Other modalities that have been proposed for the treatment of resistant PWS are the combination of PDL and 1064 nm Nd:YAG laser, and PDL and 755 nm Alexandrite laser. Experimental approaches like topical application of antiangiogenic drugs after PDL, a combination of treatment with prothrombotic or antifibrinolytic drugs encapsulated in liposomes, and the combination with photodynamic therapy are new leads in future research on this topic. In conclusion, at the chosen settings, double pass PDL at a 6 minute interval does not result in improved clearance of PWS compared to single pass laser treatment. PWS resistant to conventional PDL treatment remain a therapeutic challenge urging further research in double pass PDL therapy using various inter-pass intervals.

REFERENCES


