Improvement of disfiguring skin conditions by laser therapy
van Drooge, A.M.

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LONG-PULSED 1064 NM ND: YAG LASER IMPROVES HYPERTROPHIC PORT-WINE STAINS
ABSTRACT

Background: Hypertrophic PWS usually respond poorly to pulsed dye laser (PDL) treatment. The long-pulsed 1064 nm Nd:YAG laser can target deeper situated vessels and may therefore be more effective.

Objective: to evaluate the efficacy and safety of the Nd:YAG laser for the treatment of hypertrophic PWS.

Methods: in a retrospective cohort study, all hypertrophic PWS patients treated with the Nd:YAG laser between 2005 and 2011, were invited for follow up. Clinical improvement was assessed using Physician Global Assessment (PhGA) and Patient Global Assessment (PGA).

Results: assessment was obtained in 32 out of 44 eligible patients (mean age 51.4 years), after a mean of 2.8 (SD ± 2.1) Nd:YAG laser treatments. Good or excellent improvement of hypertrophy was found in a majority of patients, both by PhGA (91%) and PGA (93%). Good or excellent improvement of colour was found in 63% of patients by PhGA, and in 87% by PGA. Recurrence of hypertrophy was seen in 3 patients. All but two patients would recommend Nd:YAG treatment to other patients. Mild to moderate scars were seen in 7 patients, hypopigmentation in 14 patients.

Conclusion: the 1064 nm Nd:YAG laser is highly effective in the treatment of hypertrophic PWS with only a few treatments needed. Mostly mild side effects were seen in half of all patients. Hypertrophy seems to respond better than colour. To further improve colour, a combination with PDL treatment is advisory. Observation of immediate clinical endpoints is important when using the Nd:YAG laser, to optimize outcomes and reduce side effects.
INTRODUCTION

Port-wine stains (PWS) are congenital capillary malformations occurring in 0.3% of all newborns.\textsuperscript{1} Being often pink and flat at birth, PWS darken and become thicker and more nodular over time due to progressive ectasia.\textsuperscript{2-4} For the treatment of PWS, pulsed dye laser has been the standard of care since its introduction in the early 1980’s.\textsuperscript{5} Clinical studies have shown the 585 nm and the 595 nm pulsed dye laser (PDL) to be effective in the treatment of especially flat and pink or red PWS.\textsuperscript{6-8} However, PDL treatment tends to be less effective in hypertrophic PWS.\textsuperscript{9-11} Reasons for this ineffective response may include the impossibility to reach deeper situated vessels due to optical shielding of overlying superficial vessels, and the fact that light emitted by PDL has a limited penetration depth. PWS vessels have been found in the reticular plexus up to a depth of 3.7 mm.\textsuperscript{12} Histologic studies of human skin after 585 nm PDL irradiation, show complete photocoagulation of vessels of approximately 150 μm in diameter, up to a depth of approximately 0.65 mm.\textsuperscript{13,14} To reach deeper situated vessels, or to target smaller vessels, variation of PDL wavelength and/or pulse duration has been proposed.\textsuperscript{15,16} Also, studies have been done to show the effectiveness of multiple PDL passes.\textsuperscript{17,18} As a treatment option for deeper situated vascular lesions, Groot et al. described the 1064 nm Nd:YAG laser.\textsuperscript{19} In 2005, Yang et al. performed a study in which 17 patients with PWS were treated with either PDL or Nd:YAG laser.\textsuperscript{11} They found that selective photothermolysis of microvessels can be achieved at a much greater depth by 1064 nm Nd:YAG laser. However, it was difficult to use effective irradiation without causing scars. PDL-treated PWS can redarken in the course of time.\textsuperscript{20-22} The long-term effect of Nd:YAG treatment has not been evaluated yet. The aim of our study was to evaluate the safety and efficacy of Nd:YAG laser treatment in hypertrophic PWS and to assess the results of Nd:YAG laser therapy on colour and hypertrophy after a long-term follow up.

METHODS

Patients

In this retrospective cohort study, we identified all patients with hypertrophic PWS visiting the Netherlands Institute for Pigment Disorders between September 2005 and June 2011. Of these, we selected all patients who were treated at least once with the long pulsed 1064 nm Nd:YAG laser in the hypertrophic part of the PWS. Patients were eligible when pre-treatment photographs were available and when a follow up period of at least 6 months since last Nd:YAG treatment had passed. All eligible patients were invited by a letter to visit our outpatient clinic for follow up. Case charts were reviewed for history of the PWS, for previous laser treatments and number of laser treatments of the hypertrophic part of the PWS with the Nd:YAG laser. Also, other treatments performed on the hypertrophic part of the PWS since the last Nd:YAG laser treatment were registered. Hypertrophy was classified as either nodular, describing the papules and nodules arising in PWS, or as diffuse thickened, describing the larger plaques in PWS.\textsuperscript{23}
**Intervention**

A long-pulsed 1064 nm Nd:YAG laser (Mydon, Quantel-Derma, Erlangen, Germany) was used in all patients for the hypertrophic part of their PWS. Epidermal cooling was achieved by a stainless steel handpiece with an optically clear sapphire window in which a cooling liquid circulates. Cooling is improved by application of gel. Treatment was performed with a 5 mm spot size, a pulse duration of 30 ms and a fluence between 100-240 J/cm². In two patients we used a different pulse duration (15 ms and 40 ms) and in one patient we used a 7 mm spot size. In larger hypertrophic PWS, test spots were performed before starting treatment. Full treatment was started 10 to 12 weeks later. We used immediate clinical endpoints to adjust radiant exposure. Mild to moderate purpura indicated a proper tissue reaction while a greyish colour indicated overtreatment and risk of scarring. We strived for a treatment without overlap of pulses.

**Outcome measures**

The clinical assessment of the treatment response was performed by an investigator not committed to the previous treatment, using the Physician Global Assessment (PhGA). Digital photographs of the PWS taken before treatment were evaluated and compared to current clinical appearance of the lesion. Improvement was assessed by using a scale from 0-3 (0 = no improvement, 1 = moderate, 2 = good, 3 = excellent) and side effects (hyper- and hypopigmentation, scarring) were also assessed by using a scale from 0-3 (0= no side effects, 1= mild side effects, 2= moderate, 3 = severe). Also, the type (nodular, diffuse thickened, or a combination of the both) and the degree (mild, moderate, severe) of hypertrophy was assessed. Patients were asked to evaluate the improvement of the hypertrophic part of their PWS by using the Patient Global Assessment (PGA). They were asked to score the improvement for colour and thickening on a scale from 0-3 (0 = no improvement, 1 = moderate, 2 = good, 3 = excellent).

All outcomes refer specifically to the hypertrophic parts in the PWS that were treated with the Nd:YAG laser.

**Statistical analysis**

Continuous variables were presented as means with standard deviations. For the correlation between type and degree of hypertrophy and the improvement after laser therapy, we used the Fisher’s exact test. For the statistical analysis of our results we used SPSS software version 16.0 (Statistical Package for the Social Sciences. Chicago, IL, U.S.A. SPSS Inc.).

**RESULTS**

Of all 70 patients with hypertrophic PWS known in our institute, 44 patients had received Nd:YAG laser treatment. Of these, five patients refused to participate in our study for unknown reasons, two patients had moved abroad, and three patients were not able to visit us due to personal reasons not related to the previous laser treatment. Of two other patients we did not have the current address or telephone number, they
could therefore not be invited to participate in this study. In summary, a total of 32 patients (73%) were able to participate.
Eleven male and twenty-one female patients were recruited (ratio 1:1.9), with Fitzpatrick skin types I-III and a mean age of 51.4 (SD ± 16.4) at time of follow up. Before Nd:YAG laser treatment was started, other laser treatment had been performed in 24 patients, of which 18 received more than three treatments. One patient only received radiotherapy in the past, and 7 patients did not receive any treatment.
The hypertrophic port-wine stains treated with the Nd:YAG laser were mainly located on the face (20 patients), followed by neck in 7 patients, trunk in 3 patients and extremities in 2 patients. Hypertrophy was mostly of the nodular type (in 20 patients); diffuse thickening was seen in 8 patients and a combination of the both in 4 patients. The degree of hypertrophy was classified as mild in 9 patients, moderate in 18 patients and severe in 5 patients.
The mean number of Nd:YAG laser treatments of the hypertrophic part of the PWS was 2.8 (SD ± 2.1) and in 13 cases only one treatment was sufficient. The shortest follow up period since the last Nd:YAG treatment was 6 months, the longest follow up period was 71 months (mean follow up was 37 months, SD ± 20).
The Physician Global Assessment showed good or excellent improvement of the hypertrophy in 29 out of 32 patients (91%), good or excellent improvement of colour of the hypertrophy was scored in 20 out of 32 patients (63%). Mild or moderate hypopigmentation after laser irradiation was reported in 14 patients and scarring in 7 patients, of which 5 also had hypopigmentation (Table 1; Figure 1-2). Radiant exposure in patients with side effects (a mean of 144 J/cm2) was comparable to that in patients without side effects (a mean of 157 J/cm2).
There was no correlation between types of hypertrophy (nodular, diffuse thickened or a combination of the both) and the improvement of hypertrophy and colour after Nd:YAG laser therapy (p=0.18 and p=0.33 respectively; Fisher’s exact test). Also the correlation between degree of hypertrophy (mild, moderate, severe) and the improvement of hypertrophy and colour after Nd:YAG laser therapy was not significant (p=0.24 and p=0.53 respectively; Fisher’s exact test).

Table 1. Physician Global Assessment

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<td>Colour</td>
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<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Hypertrophy</td>
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<td>3</td>
<td>6</td>
<td>23</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
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<td>0</td>
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</tr>
<tr>
<td>Hypopigmentation</td>
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<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Scarring</td>
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<td>6</td>
<td>1</td>
<td>0</td>
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</table>

These are the scores given by an independent investigator.
(-: no improvement or absence of adverse reaction, +: mild improvement or mild adverse reaction, ++: good improvement or moderate adverse reaction, +++: excellent improvement or severe adverse reaction)
Patients scored good or excellent improvement of the hypertrophic port-wine stain in 26 out of 30 cases (87%). Two patients were not able to score the improvement of their PWS because it was located on the back of their body. Particularly improvement of the hypertrophy itself was scored positively (93% of patients) but also colour had improved after Nd:YAG laser treatment, according to 26 out of 30 (87%) patients. Six patients reported mild hypopigmentation or mild scarring as an adverse reaction of the laser irradiation (Table 2). This was also objectified by the physician. Two patients
would not recommend this therapy to other patients with hypertrophy in their PWS. Both patients were the only two to report mild scarring after laser therapy. After a follow up period of 27, 30 and 42 months respectively, three patients found that the previously treated hypertrophy had recurred to some degree. Also, one other patient found new nodular hypertrophy in his PWS where Nd:YAG laser was never used, 48 months after his final laser treatment.

In the follow up period after the final Nd:YAG laser treatment, eight patients had received 1 treatment with a 595 nm PDL on the hypertrophic part of the PWS to further improve colour of the PWS. Two other patients had received 3 treatments, one patient 4, and two patients 6 PDL treatments post Nd:YAG (mean number of treatments is 2.3, SD ± 1.9). Of these 13 patients, 100% had scored a good or excellent improvement of hypertrophy and 79% had scored a good or excellent improvement of colour, in the period after Nd:YAG laser treatment. Of the other 19 patients, who did not receive any other treatment of the PWS after the last Nd:YAG laser treatment, 84% had scored a good or excellent improvement of hypertrophy and 53% had scored a good or excellent improvement of colour, in the period after Nd:YAG laser treatment.

DISCUSSION
This is the first large case series showing the long term effect of the long-pulsed 1064 nm Nd:YAG laser on hypertrophic PWS. We demonstrate that hypertrophic PWS respond favourably to Nd:YAG laser therapy. This result was achieved after a mean of only 2.8 treatments, which is clearly less than the number of treatments that are usually necessary with the PDL.

Consistently, both PhGA and PGA showed excellent results for the improvement of hypertrophy, and good results for the improvement of colour. The physician found a greater improvement of hypertrophy than of colour. A previous study comparing Nd:YAG laser with PDL, also showed that improvement of hypertrophy had been promising.

Table 2. Patient Global Assessment

<table>
<thead>
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<th>n=30*</th>
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</thead>
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<tr>
<td>Colour</td>
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<td>4</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Hypertrophy</td>
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<td>1</td>
<td>10</td>
<td>18</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
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<td>0</td>
</tr>
<tr>
<td>Hypopigmentation</td>
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<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Scarring</td>
<td>28</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

These are the scores given by each patient.
* = 2 out of 32 patients could not assess the improvement of their PWS due to the location of the lesion.
(-: no improvement or absence of adverse reaction, +: mild improvement or mild adverse reaction, ++: good improvement or moderate adverse reaction, +++: excellent improvement or severe adverse reaction)
after Nd:YAG treatment while improvement of colour had been comparable to PDL treatment. For an optimal treatment of hypertrophic PWS, the combination of both Nd:YAG laser for the hypertrophy, and the PDL for the colour, should be considered. Our patients were very satisfied with the results of the Nd:YAG laser on the hypertrophic part of their PWS and all but two patients would recommend this treatment to others. Only six patients reported minor side effects. The physician however reported minor side effects in 16 patients. An explanation for this large difference can be the expertise of the physician to observe hypopigmentation and/or scarring, or perhaps the fact that patients were so satisfied with the improvement of colour and/or hypertrophy that they ignored the side effects arisen in the treated area. In the study by Yang et al. only 1 out of 17 patients developed scarring after Nd:YAG treatment. However, only minimal purpura dose was used to determine the minimal effective radiant exposure (40-250J/cm2). Also, only 2 out of 17 patients had hypertrophic PWS. We believe that hypertrophic PWS are at a higher risk for adverse reactions after Nd:YAG treatment. In our study, careful observation of the immediate clinical tissue response was necessary to adjust radiant exposure in each patient individually. Moreover, we adjusted the radiant exposure even at one single session to account for intralesional heterogeneity. We increased radiant exposure until mild to moderate purpura were seen. Generally, more hypertrophic parts with more target were treated with a lower radiant exposure (120-160J/cm2). Parts with less target were treated more aggressively (160-240 J/cm2). We intended to treat each patient with 30 ms pulse duration and a 5 mm spot size. There is no evidence from the literature to indicate the optimal pulse duration in the treatment of hypertrophic PWS with a Nd:YAG laser. In order to facilitate the evaluation of the immediate clinical endpoints as a function of radiant exposure, we chose a fixed pulse duration. In the treatment of PWS with the long-pulsed Nd:YAG laser, there is a very small therapeutic window. With only little alteration of fluence, hypopigmentation or scarring can occur. In our study, this was seen in 16 patients, which is a number that should not be ignored. We did not see any relation between radiant exposure and adverse effects, which underlines that there is no safe threshold for the long-pulsed Nd:YAG laser. Reasons why some PWS patients did develop scarring or hypopigmentation and others did not, can involve the oxygenation of the PWS, perfusion rate, vessel density or vessel depth, or perhaps the size or location of the PWS. Also, the patients’ skin type can attribute to these adverse effects. In this study, a long mean follow up, exceeding three years, was attained. In this period, only three patients had recurrence of their hypertrophy (after a follow up period of 27, 30 and 42 months). None of these three patients had received any treatment since their last Nd:YAG treatment. Of the other patients, 13 did receive one or more PDL treatments in the area previously treated with Nd:YAG. All these patients scored a good or excellent improvement of hypertrophy and colour after a long follow up period in the PhGA. Consequently, one or more PDL treatments after the last Nd:YAG laser treatment in the previously hypertrophic part of the PWS may prevent early recurrence of the hypertrophy. There are some limitations to this study. First of all, this cohort study has partly retrospectively generated data that may be unreliable. Secondly, a selection bias
caused by the fact that data come from a tertiary laser centre, results in the inclusion of more difficult to treat hypertrophic PWS that did not respond to previous PDL therapy. The female preponderance is probably also the effect of a selection bias. There was only one observer to score the improvement in our patients. Perhaps, a second observer would have reduced any bias. Also, standardized conditions were lacking in all baseline photographs. Therefore, improvement of the PWS in clinical appearance may have been difficult to score. Another limitation is the fact that not all patients treated with the Nd:YAG laser participated in this study (12 patients, 27%). Although the reasons for not participating were clearly not related to laser treatment in 7 out of 12 patients, we can not exclude some kind of selection with regard to treatment response. Finally, a significant part of the patients (41%) was treated with a PDL in the follow up period, which may have accounted for part of the improvement. However, most of these patients received only one single PDL treatment.

Previous studies have investigated the treatment of hypertrophic PWS using different settings of PDL, long-pulsed Nd:YAG laser, CO₂ laser, (long-pulsed) alexandrite laser and photodynamic therapy (PDT), all with various outcomes. Recently, also the combination of a 595 nm PDL and 1064 nm Nd:YAG laser (dual layer technique) has been proposed in the treatment of recalcitrant and hypertrophic PWS. Alster et al. found a further improvement of darker, thicker and/or nodular PWS after a series of treatments with the combined laser. A histochemical study of five patients showed better results after a dual approach (PDL and Nd:YAG laser) than PDL alone. Both studies however found an increased risk of unwanted thermal injury of the skin. A very recent in vivo study on selective photothermolysis comparing oxyhemoglobin with deoxyhemoglobin as target chromophores, showed that the 1064 nm Nd:YAG laser tends to be more selective for arterial blood. This implies that overall blood flow to the skin is targeted by the laser, and that not only photothermolysis of the target of interest occurs. Extreme caution is necessary due to a higher tendency for scarring. In 2011, Chang et al. reported four patients with nodular hypertrophy in their PWS to respond well to a total of three treatments with the 1064 nm long-pulsed Nd:YAG laser. However, they did not report any follow up in time.

In conclusion, the 1064 nm Nd:YAG laser is highly effective in the treatment of hypertrophic PWS with only a few treatments needed. However, mostly mild side effects were seen in half of all patients. To further improve the colour of both the hypertrophic part of the PWS and the surrounding macular PWS, a combination with PDL treatment is advisory. Furthermore, PDL treatment of the PWS after complete clearance of the hypertrophy by the 1064 nm Nd:YAG laser, might prevent recurrence of hypertrophy in the PWS. We do want to stress the importance of the observation of the immediate clinical endpoints while using this laser with a small therapeutic window, to optimize outcomes and reduce side effects.
REFERENCES

23. van Drooge AM, Beek JF, van der Veen JPW et al. Hypertrophy in port-wine stains: prevalence and patient characteristics in a


