A pilot study showing pulsed-dye laser treatment improves localized areas of chronic atopic dermatitis


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Abstract

BACKGROUND: Eczematous skin changes overlying port-wine stains have been reported to improve with pulsed-dye laser (PDL) treatment. However, PDL has not as yet been evaluated for the treatment of atopic dermatitis (AD; eczema). AIM: To evaluate in a controlled trial the effects and safety of PDL treatment in children with AD who had chronic localized lesions. METHODS: Twelve children with localized, chronic eczema were treated with PDL (595 nm), with untreated areas used as an intrapatient control. Treatment was given at baseline and patients were followed up at 2 and 6 weeks. Clinical outcome measures were localized Eczema Severity Score (ESS), a visual analogue scale (VAS) indicating eczema severity assessed by photographs, and adverse events. RESULTS: After 2 and 6 weeks, a significant decrease in ESS was seen for the PDL-treated areas compared with the control areas (mean +/- SEM reduction in ESS 7.0 +/- 1.0 vs. 3.3 +/- 0.8 at 2 weeks, P = 0.003, and 7.8 +/- 1.4 vs. 4.9 +/- 1.3 at 6 weeks, P = 0.002). A significant difference in eczema severity assessed by VAS at 6 weeks was seen in favour of PDL (mean +/- SEM improvement 78% +/- 20% vs. 52% +/- 10%, P = 0.003). Treatment was well-tolerated. CONCLUSIONS: In this pilot study, PDL treatment was effective in treating small areas of chronic localized eczema. This may suggest that in AD dermal vasculature plays an important role or that PDL may have an effect on cutaneous immunological activation.
Title: A pilot study showing pulsed dye laser treatment improves localized areas of chronic atopic dermatitis

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The study protocol was approved by the local Research Ethics Committee (REC).

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Summary:

Background: Eczematous skin changes overlying port-wine stains have been reported to improve with pulsed dye laser (PDL) therapy. However, PDL has not been evaluated for the treatment of atopic dermatitis (eczema) as yet.

Aim: To evaluate the effects and safety of PDL treatment in children with atopic dermatitis who had chronic localized lesions in a controlled trial

Methods: Twelve children with localized, chronic eczema were treated with PDL (595 nm) in comparison with untreated areas as an intrapatient control. Treatment was given at baseline and patients were seen thereafter at 2 and 6 weeks. Clinical outcome measures were a localized eczema severity score (ESS), a visual analogue scale (VAS), indicating eczema severity assessed by photographs, and adverse events.

Results: After 2 and 6 weeks a significant decrease in ESS was seen in the PDL group in comparison to the control group (mean reduction in ESS (± SEM) 7.0 ± 1.0 vs. 3.3 ± 0.8 at 2 weeks, \( P=0.003 \), and 7.8 ± 1.4 vs. 4.9 ± 1.3 at 6 weeks, \( P=0.002 \)). A significant difference in eczema severity assessed by VAS at 6 weeks was seen in favour of the PDL group (mean improvement (± SEM) 78% ± 20% vs. 52% ± 10%, \( P=0.003 \)). Treatment was well tolerated.

Conclusion: In this pilot study PDL therapy was effective in treating small areas of chronic localized eczema. This may suggest that in atopic dermatitis dermal vasculature plays an important role or that PDL may have an effect on cutaneous immunological activation.
Introduction

The pulsed dye laser (PDL) is based on the concept of selective photothermolysis. This technique is characterized by inducing selective damage to cutaneous blood vessels at 0.5 to 1.2 mm depth while minimizing injury to the surrounding skin structures.\(^1\) It is routinely used for treating cutaneous capillary malformations (port-wine stains). However, increasing evidence supports PDL for the treatment of other, predominantly inflammatory skin conditions, such as psoriasis, acne vulgaris and inflammatory linear verrucous epidermal naevus (ILVEN).\(^2-8\) This is the first report of using PDL to treat atopic dermatitis (eczema). We and others have previously reported a good response of eczematous skin changes overlying port-wine stains to PDL treatment in children, suggesting that the superficial dermal microvasculature may contribute to the pathogenesis of eczema.\(^9,10\) We therefore aimed to further investigate the role of PDL in atopic dermatitis. With this pilot study we evaluated the effects and safety of a single PDL treatment in patients with localized areas of eczema in a controlled setting.

Methods

Patients

The study was performed at Great Ormond Street Hospital for Children over a time period of 12 months. Children were included if they had localized, chronic, refractory discoid/nummular areas of eczema and fulfilled the Hanifin and Rajka diagnostic criteria for atopic dermatitis.\(^11\) Patients were excluded if they had received any systemic therapy other than antihistamines for their eczema one month prior to the start of the study. Children with port-wine stains who also had atopic dermatitis and discoid areas of eczema elsewhere on the body were included in this study. Written informed consent was obtained from the children’s parents. The study protocol was approved by the Local Research Ethics Commitee.
Study design and treatment

One week prior to laser treatment all patients had to completely stop their previous topical eczema therapy. They were instructed to exclusively use an emollient containing cetomacrogol 2.25%, cetostearyl alcohol 7.2%, liquid paraffin 6% and white soft paraffin 15% (Diprobase cream®; Schering-Plough) twice daily for the entire study period (one week before and 6 weeks after PDL). At the initial visit one to three localized areas of eczema measuring 2-3 centimeters in diameter were selected for treatment with PDL. Similar areas of eczema in terms of size and clinical severity were selected on the contralateral side of the body as the control sites. In patients with no similar contralateral areas of eczema the selected sites were divided and one half was treated with PDL and the other half served as the control. One session of PDL treatment (Vbeam vascular pulsed dye laser manufactured by Candela Corporation, Wayland, Massachusetts, USA) was performed to the selected areas in combination with the use of an integrated cryogen cooling system (Dynamic Cooling Device, DCD). A wavelength of 595 nm and a spot size of 7 mm were consistently used in all patients. The laser fluences and pulse duration were chosen according to the individual skin response as assessed by a test treatment to normal uninvolved skin, usually on the forearm, using fluences of 4, 4.5 and 5 J cm$^{-2}$. The fluency which produced the earliest sign of erythema/purpura was then multiplied by a factor of 2 and used as the initial treatment fluence. This is our standard protocol for all PDL treatments using the Vbeam laser at Great Ormond Street Hospital. The setting of the integrated cooling device was fixed at 30 milliseconds for both spray duration and delay duration unless the laser fluency levels reached more than 12 J cm$^{-2}$, in which case the duration was increased. Local anaesthesia was obtained using the topical application of a cream containing lidocaine 2.5% and prilocaine 2.5% (EMLA®, AstraZeneca). On the control eczema areas, EMLA® cream and the cryogen cooling device were applied. If the laser treatment was performed under general anaesthesia, as for children who were having PDL treatment for port-wine stains elsewhere on their body, no EMLA® cream was used either on the treated and the control area.

Following laser treatment the patients had a follow-up review at 2 and 6 weeks.
**Clinical outcome measures**

For the clinical assessment of the eczema areas we used a localized eczema severity score (ESS). This was based on a modification of the validated eczema area and severity index (EASI) and the six area, six sign atopic dermatitis (SASSAD) severity.\textsuperscript{12,13} Our localized ESS was the sum of the scores of 6 clinical signs (erythema, edema/induration/papulation, excoriations, oozing/weeping/crusting, scaling and lichenification), these being graded from 0 to 3 (0, absent; 1, mild; 2, moderate; 3, severe), giving a maximum score of 18. It was not possible to accurately assess pruritus specific to these small areas of eczema. The lesions were scored at baseline (pre-PDL treatment) and after 2 and 6 weeks. Photographs of the selected areas were taken at baseline and repeated after 6 weeks. These were assessed by a physician blinded to the study intervention. The eczema severity between baseline and 6 weeks was noted on a linear visual analogue scale (VAS) and changes reported in percentages. The children’s parents were asked to report any adverse events.

**Statistical analysis**

Values are given as mean ± standard error of the mean (SEM) or percentages. Values from multiple sites per patient were averaged. Data were tested for normality by analyzing histograms and Q-Q plots, which looked roughly normal. In addition squewness and kurtosis of eczema severity scores were within the +2 and -2 range for controls and treated areas, respectively. Hence, comparisons between groups were made with the paired t-test. P < 0.05 was considered to be statistically significant. The analyses were performed with the use of Data Desk 6.2.1 (Data Description Inc.). Advice and analysis of this data was performed by Professor Tim Cole, Head of Biostatistics at the Institute of Child Health, London.

**Results**

**Patients and treatment**
Fifteen children were enrolled in the study. Due to a flare of eczema two patients had to be excluded before the laser treatment could be performed. Another patient was unable to attend any of the follow-up visits and was therefore excluded from the analysis. Hence, the data of 12 children were included in the study. In eight of them only one eczema lesion was selected and lasered whereas for the remaining four children, three eczema sites each were treated. Thus, a total of 20 eczema areas and 20 corresponding control sites were included in the study. The patient characteristics and the location of the eczema lesions are shown in Table 1. The mean age of the patients was $6.5 \pm 1.2$ years (minimum 2, maximum 14 years). Seven children had a port-wine stain elsewhere on the body which was treated with PDL during the same session. The laser treatment was performed under local and general anaesthesia in 7 and 5 patients, respectively. The laser fluences and pulse duration used ranged from 5 to 13 J cm$^{-2}$ and 1.5 and 6.0 milliseconds, respectively. Two children were unable to attend the 2-week-follow-up and one other patient missed the 6-week-follow-up.

**Clinical outcome**

The patient characteristics and changes in local ESS and VAS following laser therapy are listed in Tables 1 and 2. In all but one patient (no. 7) the lasered eczema lesions improved substantially more than the control areas (Fig. 1). After 2 and 6 weeks the mean ESS decreased significantly in the treated eczema lesions in comparison with the control sites ($P=0.003$ and $P=0.002$, respectively). Figure 2 demonstrates the ESS for the PDL and control group over time. There was a greater than 75% improvement at 8/18 of the treated sites at 2 weeks and 13/17 sites at 6 weeks. Complete clearance (100%) occurred at 2/18 sites (2 patients) at 2 weeks and 9/17 sites (7 patients) at 6 weeks. Complete clearance was also observed in 2 corresponding control sites of the 9 areas that cleared completely 6 weeks after PDL treatment (Table 1).
The change in eczema severity assessed by VAS at 6 weeks showed a better improvement of the treated lesions in comparison with the control areas (mean change in VAS from baseline 78% ± 11% and 52% ± 10% in the PDL and control group, respectively, \( P=0.003 \)). There was no significant difference in response for the control sites between those children who had a general anaesthesia and did not have EMLA® cream and those who received local anaesthesia with EMLA® cream (at 2 weeks: mean decrease in ESS 3.4 ± 1.2 in the EMLA® group vs. 3.0 ± 0.6 in the non-EMLA® group, \( P=0.844 \); at 6 weeks: mean decrease in ESS 6.2 ± 1.6 in the EMLA® group vs. 3.4 ± 1.9 in the non-EMLA® group, \( P=0.293 \) and mean change in VAS 58% ± 11% in the EMLA® group vs. 46% ± 18% in the non-EMLA® group, \( P=0.574 \)).

**Adverse events**

Two patients who had local anaesthesia for their PDL treatment reported mild discomfort and pain during the intervention. There was no blistering or pigmentary change in any of the lesions following treatment. Patient no. 7, who showed a deterioration of his eczema by 6 weeks, was found to have a superinfection with candida albicans at the treated site, which responded rapidly to topical therapy.

**Discussion**

In this pilot study, children with localized chronic areas of atopic dermatitis were treated with the PDL in an open, intrapatient controlled comparison. After 2 and 6 weeks there was significant improvement of the treated eczema lesions in comparison with the control areas. No major adverse events were detected apart from mild discomfort during the procedure. To our knowledge this is the first study describing the use of PDL for the treatment of atopic dermatitis. The management of eczema entails different approaches, depending on the severity, extent and distribution of the skin lesions and other patient characteristics, such as age and compliance. Current treatment strategies include emollients, anti-inflammatory...
agents, immune modulators, immunosuppressants, antimicrobials, antihistamines and phototherapy.\textsuperscript{14}

The concept of treating eczema by targeting directly cutaneous blood vessels with the PDL is new and was proposed following our experience with PDL in children with eczema overlying port-wine stains. We\textsuperscript{9} reported complete clearance of eczema in the area of port-wine stains in 12 and a definite improvement in 2 out of 15 children treated with PDL. In the report of Tay \textit{et al}.\textsuperscript{10} PDL treatment led to permanent clearance of eczema overlying port-wine stains in 2 children.

PDL has been shown to have a positive effect in other inflammatory skin disorders, such as acne vulgaris, psoriasis and inflammatory linear verrucous epidermal naevus (ILVEN).\textsuperscript{2-8} Low-fluence (non-ablative) PDL therapy led to substantial improvement of inflammatory acne in a double-blind, randomised controlled trial.\textsuperscript{7} High fluences cause ablation of small blood vessels and purpura whereas low fluences do not. The underlying mechanism of non-ablative PDL in acne is suggested to be damage to sebaceous glands and/or propionibacterium acnes and the increase in immunosuppressive cytokines, which promote a reduction in inflammation.\textsuperscript{15} In psoriasis, where morphologic changes of the superficial dermal vasculature are a distinct feature, PDL treatment was shown to be beneficial and superior to potent topical therapy with calcipotriol/betamethasone dipropionate.\textsuperscript{2}

Immunohistochemical evaluation of psoriatic plaques following conventional PDL showed a reduction in endothelial surface area, endothelial cell proliferation and CD4+ and CD8+ T-cell infiltrate in the superficial dermis.\textsuperscript{4} This suggests that expanded capillaries may be important in facilitating the access of activated T lymphocytes and therefore maintaining disease activity in psoriatic plaques.

The role of the skin vasculature in atopic dermatitis has recently been highlighted.\textsuperscript{16} Eczema lesions are characterized by differences in the activation state of endothelial cells and the release of inflammatory mediators. Thus blood vessels are central to the regulation of inflammatory responses of atopic dermatitis. The understanding of these mechanisms could explain the positive effect of PDL in eczema lesions. We believe that by reducing the
underlying vasculature, PDL treatment leads to a decrease in the dermal inflammatory infiltrate which ultimately results in an improvement of the eczema. It remains unclear whether conventional PDL not only affects the skin by selective photothermolysis but also by direct cutaneous immunological activation, as demonstrated in a recent study for low-fluence PDL (Chromogenex V3). Phototherapy, such as narrow-band UVB light (311-313 nm), is well known to be effective against atopic eczema by stimulating an immunological response in the skin. Targeted phototherapy using a 308 nm xenon chloride excimer laser has recently been shown to be effective in treating localized atopic dermatitis.

This study was designed as a pilot study and therefore includes a small number of patients. Other limitations are the lack of immunohistochemical evaluation, a study design which was not randomised nor blinded and the use of variable laser fluences. Blinded studies are difficult to undertake with high-fluence PDL because of the immediate development of visible skin changes or pain which hinder masking. Different laser fluences were chosen in order to achieve a consistent effect of treatment in each patient according to their individual skin responses. In patients where the selected area of eczema was divided in half for PDL and control some therapeutic "carry-over" effect from the PDL to the non-treated area could be suspected. Despite this potential bias the difference between the PDL and control group remained highly significant.

Laser treatment for atopic dermatitis is not a practical option but it may be useful for stubborn small areas of discoid eczema as an alternative to using potent topical steroids or topical calcineurin inhibitors. However, we believe that the main value of this study has been to further support the fact that endothelial cells play a key role in the pathophysiology of atopic dermatitis and that more research along these lines is important to improve our understanding of this condition and for the development of new treatments.

Acknowledgments
The authors wish to thank Candela Corporation (Wayland, Massachusetts, USA) for providing the Vbeam vascular pulsed dye laser for the period of this study and Professor Tim Cole, Institute of Child Health, for the statistical support. Dr. Lisa Weibel was supported by a nonrestricted grant from the Stiefel-Zangger Foundation, the Novartis Foundation and Spirig Pharma AG, Switzerland.
References


Table 1 Patient characteristics and clinical response to study intervention over a 6 week period

<table>
<thead>
<tr>
<th>Patient (n=12)</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Site of eczema lesions (PDL and control)</th>
<th>% Improvement of local eczema severity score</th>
<th>% Improvement of VAS for eczema severity by photographs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 weeks PDL/Control</td>
<td>6 weeks PDL/Control</td>
</tr>
<tr>
<td>1</td>
<td>M</td>
<td>5</td>
<td>Ankle</td>
<td>67/0 PDL/Control</td>
<td>89/28 PDL/Control</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Calf</td>
<td>53/22 PDL/Control</td>
<td>33/6 PDL/Control</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Knee</td>
<td>18/-7 PDL/Control</td>
<td>64/40 PDL/Control</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>12</td>
<td>Arm</td>
<td>56/0 PDL/Control</td>
<td>100/33 PDL/Control</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>5</td>
<td>Leg</td>
<td>71/29 PDL/Control</td>
<td>100/43 PDL/Control</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>7</td>
<td>Arm</td>
<td>88/50 PDL/Control</td>
<td>100/100 PDL/Control</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>2</td>
<td>Eyelid</td>
<td>17/33 PDL/Control</td>
<td>75/67 PDL/Control</td>
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<tr>
<td>6</td>
<td>F</td>
<td>2</td>
<td>Cheek</td>
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<td>88/88 PDL/Control</td>
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<td>F</td>
<td>2</td>
<td>Neck</td>
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<td>-60/-60 PDL/Control</td>
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<td>8</td>
<td>F</td>
<td>14</td>
<td>Hand</td>
<td>46/54 PDL/Control</td>
<td>62/62 PDL/Control</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>Arm</td>
<td>62/23 PDL/Control</td>
<td>100/54 PDL/Control</td>
</tr>
<tr>
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<td></td>
<td>Arm</td>
<td>69/31 PDL/Control</td>
<td>100/62 PDL/Control</td>
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<tr>
<td>9</td>
<td>M</td>
<td>8</td>
<td>Calf</td>
<td>92/17 PDL/Control</td>
<td>- PDL/Control</td>
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<tr>
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<td></td>
<td></td>
<td>Knee</td>
<td>75/19 PDL/Control</td>
<td>- PDL/Control</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Knee</td>
<td>75/19 PDL/Control</td>
<td>- PDL/Control</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>3</td>
<td>Arm</td>
<td>100/40 PDL/Control</td>
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<tr>
<td>11</td>
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<td>10</td>
<td>Eyelid</td>
<td>- PDL/Control</td>
<td>100/29 PDL/Control</td>
</tr>
<tr>
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<td>F</td>
<td>8</td>
<td>Leg</td>
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<td>100/56 PDL/Control</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td>94/81 PDL/Control</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Leg</td>
<td>100/69 PDL/Control</td>
<td>100/100 PDL/Control</td>
</tr>
</tbody>
</table>

PDL, pulsed dye laser; VAS, linear visual analogue scale; - indicates that follow-up information could not be obtained;
% Improvement at 2 weeks and 6 weeks are compared with baseline; negative %-values indicate deterioration of the lesion.
Table 2 Local eczema severity score (ESS) at baseline and 2 and 6 weeks after study intervention

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n=12)</th>
<th>2 weeks (n=10)</th>
<th>6 weeks (n=11)</th>
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<tr>
<td></td>
<td>ESS</td>
<td>ESS</td>
<td>Improvement in ESS from baseline</td>
</tr>
<tr>
<td>PDL</td>
<td>10.0 ± 1.1</td>
<td>3.9 ± 1.0</td>
<td>7.0 ± 1.0</td>
</tr>
<tr>
<td>Control</td>
<td>10.1 ± 1.2</td>
<td>7.7 ± 1.3</td>
<td>3.3 ± 0.8</td>
</tr>
</tbody>
</table>

Data shown as mean ± SEM; *change from baseline for PDL vs control group; PDL, pulsed dye laser.
Figure legends

Figure 1
a) Clinical photograph of a localized, chronic eczema lesion at the ankle of a patient (no. 1) before laser treatment. b) Six weeks later, lesion showing marked improvement in the area treated with pulsed dye laser (PDL).

Figure 2
Localized eczema severity score (ESS, range 0-18) in sites treated with pulsed dye laser (PDL) compared with untreated eczema areas (control) over time. Values are expressed as means ± SEM. The lines connecting the bars indicate statistical significance of $P<0.01$. 
