Pulsed-dye laser treatment for inflammatory acne vulgaris: randomised controlled trial

E D Seaton, A Charakida, P E Mouser, I Grace, R M Clement, A C Chu

Summary

Background Low-fluence (low irradiation energy density) pulsed-dye lasers (PDLs) have been used for atrophic acne scarring, and anecdotal experience suggests that long-term improvements in inflammatory acne can be seen after one PDL treatment. Our aim was to compare the efficacy and tolerability of such PDL treatment with sham treatment in patients with facial inflammatory acne in a double-blind, randomised controlled trial.

Methods We recruited 41 adults with mild-to-moderate facial inflammatory acne. We randomly assigned patients to PDL (n=31) or sham treatment (n=10). Treatment was given at baseline and patients were seen after 2, 4, 8, and 12 weeks. Assessors and participants were unaware of treatment allocations. Primary outcome measures were acne severity after 12 weeks and adverse events at any time. Secondary measures were change in lesion counts after 12 weeks and change in acne severity with time. Analysis was by intention-to-treat.

Findings After 12 weeks, acne severity (measured by Leeds revised grading system) was reduced from 3·8 (SD 1·5) to 1·9 (1·5) in the PDL group and 3·6 (1·8) to 3·5 (1·9) in the sham group (p=0·007). Treatment was well tolerated. Total lesion counts fell by 49% (IQR 30 to 75) in PDL patients and 9% (-16 to 38) in controls (p=0·024). The most rapid improvements were seen in the first 4 weeks after treatment.

Interpretation PDL therapy improves inflammatory facial acne 12 weeks after one treatment with no serious adverse effects.

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Introduction

Acne vulgaris is a common disease that has been associated with social isolation, employment difficulties, depression, and suicide. The many treatments that are available indicate the dissatisfaction of patients and doctors with available therapies and difficulties in management of this disease. New, effective, and well tolerated treatments are needed.

Early inflammatory acne lesions are characterised by the infiltration of the pilosebaceous duct with CD4+ T-helper-1 cells that are reactive to Propionibacterium acnes, a common cutaneous commensal. Colonisation of individuals with this bacterium is closely associated with the development of inflammatory acne, and the development of antibiotic resistance of P acnes is associated with treatment failure. P acnes is a porphyrin-containing organism that is killed by exposure to specific wavelengths of light. The photosensitivity of the bacterium accounts for the improvement noticed by most individuals with acne after exposure to sunlight, and has encouraged the development of artificial visible light sources as treatment for this disease.

Lasers differ from non-laser light sources in that they emit minimally divergent, coherent light that can be focused to a small area of tissue to provide very high irradiances. Pulsed-dye lasers (PDLs) emit visible light that is mainly absorbed by oxyhaemoglobin, so high irradiation energy densities (fluences) are used to treat vascular lesions such as port wine stains. Whereas high fluences ablate small blood vessels and cause purpura, lower non-ablative fluences do not. Low fluences can, however, stimulate cutaneous procollagen production, secondary to a non-lethal heating of dermal perivascular tissues that is postulated to alter local cellular metabolism. Non-ablative PDLs are increasingly used in cosmetic practice to improve the appearance of fine wrinkles and are effective in the treatment of atrophic acne scarring.

Experience in several clinics suggests that a proportion of patients receiving low-fluence PDL treatment have coincidental striking and longstanding improvements in inflammatory acne after a sole treatment of the face (unpublished). We aimed to examine the efficacy and tolerability of a single low-fluence PDL treatment in patients with facial inflammatory acne.

Methods

Patients

Individuals were recruited through a public request for participants or because of referral to the dermatology clinic. Recruitment took place between Nov 13, 2001, and April 26, 2002, so that confounding effects of summer sunlight were avoided. Eligible patients were aged between 18 and 45 years with mild-to-moderate facial inflammatory acne defined as the presence of at least ten acne papules or pustules between the brow and
with no active inflammatory acne were assigned a score of means of recording inflammatory acne by matching acne revised acne grading system is a rapid and reproducible acne grading, total lesion counts (inflammatory and non-

demographic details and did clinical assessments with treatment. Investigators were not only to the investigator (EDS, AC, or ACC) who was assigned to treat the patient. Investigators were not included in preliminary or post-treatment assessments of patients that they had treated.

Patients received a single treatment at baseline and were reviewed after 2, 4, 8, and 12 weeks. For every patient, one trained investigator (EDS, AC, or ACC) recorded demographic details and did clinical assessments with acne grading, total lesion counts (inflammatory and non-inflammatory lesions), inflammatory lesion counts (papules and pustules), and non-inflammatory lesion counts (open and closed comedones). The Leeds revised acne grading system is a rapid and reproducible means of recording inflammatory acne by matching acne severity with validated photographs of acne patients and assigning a numerical score between 1 and 12. Patients with no active inflammatory acne were assigned a score of zero in this trial. Although some difficulty can be encountered in patients with very localised acne and in those with pigmented skin, this technique provides a straightforward means of clinical acne classification and has become established as a grading method in many clinical trials of acne treatment. The investigators have had longstanding experience of both the use of this technique and of lesion counting which was done in all patients as an additional assessment. Lesion counts were recorded for the whole face (excluding the nose) and for each half of the face on either side of the midline. Lesion counting is a highly reproducible technique when done by a trained investigator. Possible adverse events were assessed by direct questioning of patients and by review of daily diary sheets that all patients were asked to complete.

To allow dose response to be assessed, every laser-allocated patient received treatment in which a different fluence was used on each side of the midline. Patents were randomly allocated to receive 1·5 J/cm² on one side of the midline and 3·0 J/cm² on the other. We used a PDL with a wavelength of 585 nm, laser spot diameter of 5 mm, and pulse duration of 350 μs (NLite system, EUPhotonics, Swansea, Wales, UK). Patients’ whole faces were treated in about 15 min by moving the laser handpiece from brow to jawline.

Controls were treated with a disconnected laser handpiece that was moved across the face in an identical manner to that for the PDL group. All patients wore opaque goggles during treatment to protect their eyes and to ensure that they were unaware of the therapy they received. Treatment was given in a locked room with no windows.

The primary endpoints of the study were change in acne severity after 12 weeks based on the Leeds revised grading system and adverse events at any time. Secondary endpoints were changes in total, inflammatory and non-inflammatory lesion counts by the end of the trial, and changes in acne severity with time. We also assessed the proportion of patients achieving a reduction of 1 or 2 points in acne grade or a 50% reduction in total acne lesion count by 12 weeks. Subgroup analysis of total, inflammatory, and non-inflammatory lesion counts on each side of the midline was done in laser-treated patients to allow assessment of the effect of different laser fluences.

Statistical analysis
Data conforming to a normal distribution were analysed with two-sample t tests. We analysed non-normally distributed data using Mann-Whitney U test for independent groups and Wilcoxon matched pairs signed rank test for paired data (half face comparisons). Changes from baseline are reported in absolute numbers and percentages, with statistical analyses done for absolute values. Analysis of proportional data was done with Fisher’s exact test. For the primary clinical outcome
Table 2: Acne severity and lesion counts at baseline and 12 weeks after intervention and analysed per protocol. *Change from baseline after 12 weeks for laser vs sham. tData for severity are parametrically distributed, shown as mean (SD), and for lesions are non-parametrically distributed, shown as median (IQR).

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Baseline</th>
<th>n</th>
<th>Improvement from baseline</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>(Leeds revised grade)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laser (n=31)</td>
<td>3-6 (1.5)</td>
<td>31</td>
<td>1-9 (1.8)</td>
<td>0.007</td>
</tr>
<tr>
<td>Sham (n=10)</td>
<td>4-6 (1.8)</td>
<td>10</td>
<td>0-1 (1.0)</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Total lesions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laser (n=34)</td>
<td>3-6 (1.5)</td>
<td>31</td>
<td>1-9 (1.8)</td>
<td>0.023</td>
</tr>
<tr>
<td>Sham (n=13)</td>
<td>4-6 (1.9)</td>
<td>10</td>
<td>0-1 (1.0)</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>Inflammatory lesions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laser (n=29)</td>
<td>2-12 (6)</td>
<td>31</td>
<td>6-23 (12)</td>
<td>0.024</td>
</tr>
<tr>
<td>Sham (n=10)</td>
<td>12 (1.7)</td>
<td>10</td>
<td>0-1 (1.0)</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>Non-inflammatory lesions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laser (n=17)</td>
<td>11 (5)</td>
<td>31</td>
<td>6-23 (12)</td>
<td>0.024</td>
</tr>
<tr>
<td>Sham (n=10)</td>
<td>12 (1.7)</td>
<td>10</td>
<td>0-1 (1.0)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Data for lesions are non-parametrically distributed, shown as median (IQR) and analysed per protocol. *Change from baseline after 12 weeks for laser vs sham. | Data for severity are parametrically distributed, shown as mean (SD) and analysed by intention-to-treat.

Table 3: Regression analysis to assess effect of baseline characteristics on Improvement of acne severity at 12 weeks

<table>
<thead>
<tr>
<th>Coefficient (β)</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference treatment</td>
<td>-2.22</td>
<td>-3.4 to -1.04</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment group</td>
<td>-0.003</td>
<td>-0.07 to 0.07</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment group</td>
<td>0.57</td>
<td>-1.02 to 1.04</td>
</tr>
<tr>
<td><strong>Age of onset of acne</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment group</td>
<td>-0.004</td>
<td>-0.11 to 0.07</td>
</tr>
<tr>
<td><strong>Duration of acne</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment group</td>
<td>0.013</td>
<td>-0.06 to 0.07</td>
</tr>
<tr>
<td><strong>Skin type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment group</td>
<td>-0.05</td>
<td>-0.85 to 0.36</td>
</tr>
<tr>
<td><strong>Use of oral isotretinoin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment group</td>
<td>-0.14</td>
<td>-2.10 to 1.86</td>
</tr>
<tr>
<td><strong>Use of systemic antibiotics for acne</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment group</td>
<td>-0.2</td>
<td>-1.36 to 0.96</td>
</tr>
</tbody>
</table>

Outcome difference in Leeds revised acne grading score (12 weeks minus baseline). Analysis is per protocol.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Figure 1 shows the trial profile. 26 laser-allocated patients and nine controls had volunteered for the trial independently, whereas the remainder were recruited by the investigators after referrals to the dermatology outpatient clinic. Four of 31 (13%) laser-treated patients withdrew, including two patients by 8 weeks and one by 4 weeks, all three of whom left the locality. Another laser-treated patient withdrew by 4 weeks after needing systemic antibiotic treatment for worsening truncal acne. One of ten controls withdrew by 4 weeks because of dissatisfaction with clinical response.

Tables 1 and 2 show the baseline demographic and clinical characteristics of the two groups. Most patients were young adults (38 of 41 were younger than 40 years, 31 of 41 were younger than 35 years) who had had a long history of acne. Similar proportions of patients in each group had previously received systemic antibiotics or oral isotretinoin. Most patients in both groups were white, and Asian and Afro-Caribbean ethnic groups were represented only in the laser treatment group.

The difference between the groups’ acne severity at the start of the trial was 0.2 on the Leeds revised grading system. By intention-to-treat analysis, after 12 weeks, mean acne grade had improved from baseline 1.9 (SD 1.8) in laser-treated patients and by 0.1 (SD 1.4) in patients. Our data should allow calculation of sample size for future investigations.

Sample size and allocation ratio

We used an uneven allocation ratio of 3 to 1 to facilitate assessment of the safety of this previously unreported treatment and to encourage recruitment. This design improves the probability of identifying infrequent adverse events although, inevitably, reduces the power of the study to detect differences in efficacy between groups, by an amount that is equivalent to excluding a quarter of patients. Our data should allow calculation of sample size for future investigations.

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Table 2: Acne severity and lesion counts at baseline and 12 weeks after intervention
Figure 3 shows the relation between acne severity for

*One control with multiple non-inflammatory lesions and a consequent high lesion count was excluded.

sham-treated patients (p=0.007) (table 2). Per protocol analysis and an analysis that excluded three laser-treated patients who moved from the locality and were assumed to be missing completely at random, produced similar results to the intention-to-treat analysis (reduction of acne grade from baseline for per protocol analysis, laser mean 2.1 [SD 1.5], sham 0.1 [SD 1.2], p=0.001; for analysis excluding patients missing completely at random, laser 2.1 [SD 1.6], sham 0.1 [SD 1.4], p=0.001).

Forward stepwise regression analysis failed to identify any factor other than treatment-group allocation that substantially affected the reduction in acne severity by 12 weeks (table 3). Figure 2 shows the observed mean change in overall acne severity throughout the trial. Acne severity improved at every assessment in the laser-treatment group, the most rapid improvement occurring in the first 4 weeks after treatment. Repeated measures analysis of acne severity that used all data obtained at every timepoint of the trial indicated a change in acne severity with time (p=0.001) and also with interaction between time and group allocation (p=0.001), and a slight difference between treatment groups (p=0.09). Figure 3 shows the relation between acne severity for individual patients at the start and that at the end of the trial. The figure indicates that improvements were seen in laser-treated patients who had a wide range of initial severities and included those with severe disease, such as two patients with initial severity score of 7 and final score of 1, and one with initial severity score of 6 and final score of 1. After 12 weeks, severity had improved (reduced by at least 1 point on the grading scale) in 25 of 27 laser-treated patients and two of nine controls (p=0.0001). Severity improved by at least 2 points in 16 of 27 patients treated with laser and in none of 9 controls (p=0.002).

Adverse events are shown in table 4. Six laser-treated patients and two controls reported side-effects during the trial period. Two of the 31 patients who received laser treatment had deeply pigmented Afro-Caribbean skin. Both had moderate transient discomfort during irradiation at a high fluence (3.0 J/cm²), and one described purpura that lasted 6 days on the side of the face that had been treated at this fluence. Three in the laser group and two controls reported short-term pruritus, dry skin, or dry lips.

Table 4: Adverse events

Adverse event  Laser group (n=33)  Sham laser group (n=10)  p

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Laser group (n=33)</th>
<th>Sham laser group (n=10)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain during laser</td>
<td>2*</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>treatment (3 J/cm²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient purpura</td>
<td>3*</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1</td>
<td>1†</td>
<td>0.43</td>
</tr>
<tr>
<td>Dry skin</td>
<td>1</td>
<td>2†</td>
<td>0.14</td>
</tr>
<tr>
<td>Dry lips</td>
<td>1</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>Watery eye</td>
<td>1</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>Any</td>
<td>6</td>
<td>2</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*Symptoms were seen in same patients.

Table 4: Adverse events

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Total, inflammatory, and non-inflammatory lesion counts were similar in both groups at the start of the trial (table 2). After 12 weeks, a greater improvement in total and inflammatory lesion counts was recorded in the laser-treated group (table 2 and figure 3) than in controls. Total lesion counts fell by 53% in laser-treated patients and by 9% in placebo-treated patients (p=0.023). Inflammatory lesion counts fell by 49% in laser-treated

Figure 2: Change in acne severity with time

Data are mean (SD).

Figure 3: Acne severity (A) and total lesion count (B) at baseline and 12 weeks

*One control with multiple non-inflammatory lesions and a consequent high lesion count was excluded.
The proportion of acne patients carrying strains of *P. acnes* resistant to tetracycline, erythromycin, or clindamycin rose from 34.5% to 64% between 1990 and 1997 in an urban population in the UK. At a time when prudent antibiotic prescription is being advocated in public-health initiatives to prevent the development of widespread global antibiotic resistance, the routine use of long courses of antibiotic treatment for acne should be re-assessed.

Oral isotretinoin, a synthetic retinoid with powerful effects on cellular differentiation and division, is the most effective treatment and induces long-term remissions in a proportion of patients. Indications for its use have recently broadened from nodulocystic acne to less severe forms, including mild-to-moderate disease that does not respond to systemic antimicrobials and acne associated with severe psychological problems. However, isotretinoin causes dryness of the skin and mucous membranes in most patients and has been associated with more serious adverse events including: myalgia, arthralgia, benign intracranial hypertension, hepatitis, hyperlipidaemia, acne fulminans, and visual disturbances. A possible association between isotretinoin and depression, suicide, psychosis, and violent behaviour has recently been added to product information and remains under investigation. In the USA, despite awareness of the high teratogenicity of isotretinoin and the implementation of strict guidelines governing its prescription to women, about three pregnancy exposures take place per 1000 prescriptions of the drug.

An optimum acne treatment would have longlasting effectiveness in the control of active disease, improve acne scarring, have few local or systemic side-effects, and would be acceptable to patients.

The patients in our trial are likely to have been broadly representative of adults with acne in the general population, although recruitment of volunteers might have introduced a selection bias towards those with longstanding acne that had failed conventional treatments. Masked studies are difficult to undertake with ablative lasers because the immediate development of visible skin changes or pain can severely hinder masking. However, low fluence non-ablative PDL treatment usually produces no immediately obvious changes to the skin. Two patients who had discomfort during treatment and communicated their experience to investigators might have introduced bias by suggesting their treatment allocation to investigators. Since the remaining patients reported no symptoms during treatment with non-ablative PDL, treatment allocation was probably adequately masked.

We used an intention-to-treat analysis for assessment of acne severity and to carry forward last available results in missing patients, thereby maintaining the benefits of randomisation. Repeated analyses per protocol that excluded these patients yielded similar results, suggesting that this approach was reasonable. Every laser-treated patient in the study received treatment at two different fluences (1.5 J/cm² and 3.0 J/cm²) on opposite sides of the face. The proportion of patients. Indications for its use have recently broadened from nodulocystic acne to less severe forms, including mild-to-moderate disease that does not respond to systemic antimicrobials and acne associated with severe psychological problems. However, isotretinoin causes dryness of the skin and mucous membranes in most patients and has been associated with more serious adverse events including: myalgia, arthralgia, benign intracranial hypertension, hepatitis, hyperlipidaemia, acne fulminans, and visual disturbances. A possible association between isotretinoin and depression, suicide, psychosis, and violent behaviour has recently been added to product information and remains under investigation. In the USA, despite awareness of the high teratogenicity of isotretinoin and the implementation of strict guidelines governing its prescription to women, about three pregnancy exposures take place per 1000 prescriptions of the drug.

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An optimum acne treatment would have longlasting effectiveness in the control of active disease, improve acne scarring, have few local or systemic side-effects, and would be acceptable to patients.
PDLs are also reported to be effective in the treatment of atrophic acne scarring and reduced mean scar depth by 48% after just one treatment. Our results suggest that this laser treatment could be developed as a new therapeutic approach that would allow simultaneous treatment of both active acne and associated scarring. We believe that laser treatment should be further explored as an adjuvant or alternative to daily conventional pharmacological treatments.

Contributors
R M Clement conceived the study. E D Seaton and A C Chu did most of the design study, data collection, treatment intervention, and result assessment. E D Seaton wrote the report and A C Chu revised the manuscript. I Grace provided statistical advice and analysis. A Charakida assisted with data collection, administration, and treatment intervention. P E Mouer assisted with data collection and administration.

Conflict of interest statement
Since completion of the trial, EDS has started laboratory research into the mechanism of action of PDL therapy in acne at the Department of Dermatology, Imperial College, London, UK, with financial support from EUPhotonic RMC was an academic employee of EUPhotonic, and contributed to development of the laser and trial conception, but not to detailed trial design, data collection, data analysis, or interpretation of the results. The other authors have no conflict of interest.

Acknowledgments
EUPhotonic (Swansea, Wales) provided the laser. We thank Michael Kiernan, Jay Bimbbaum, and Dougans Seaton for very helpful comments during the study, and Jean Berkeley and Jen Morris for administrative support.

References