Treatment of Xanthelasma Palpebrarum Using a Pulsed Dye Laser: A Prospective Clinical Trial in 38 Cases

SYRUS KARSAI, MD,* AGNIESZKA CZARNECKA, MD,* AND CHRISTIAN RAULIN, MD†

BACKGROUND Several studies have reported positive results of nonablative laser treatment of xanthelasma palpebrarum, but the published evidence is weak and inconclusive.

OBJECTIVE To systematically evaluate the effect of pulsed dye laser (PDL) treatment of xanthelasmas.

MATERIALS AND METHODS Twenty female Caucasian patients with 38 lesions (≤1 mm above skin level) were enrolled. They received up to five treatment sessions with a PDL (wavelength, 585 nm; energy fluence, 7 J/cm²; pulse duration, 0.5 ms; spot size, 10 mm; number of passes, 2) at 2- to 3-week intervals. Photographs were taken before each treatment session and 4 weeks after the last treatment. Two independent examiners categorized clearance into four groups (no clearance [<25% xanthelasma area(s) cleared], moderate [25–50%], good [51–75%], and excellent [>75%]). Patient satisfaction was assessed on a verbal rating scale.

RESULTS Approximately two-thirds of the lesions showed clearance greater than 50%, and one-quarter had clearance greater than 75%. Interrater reliability was excellent (contingency coefficient >0.7 at all visits). Treatments were well tolerated and had no major side effects. Patient satisfaction was generally high.

CONCLUSION PDL is a promising approach for treating xanthelasmas, especially when multiple sessions are performed.

The authors have indicated no significant interest with commercial supporters.

Xanthelasma palpebrarum consists of soft yellowish plaques on the upper or lower eyelid. It is a possible sign of some of the most common and serious internal diseases, such as hyperlipidemia, diabetes mellitus, liver cirrhosis, and myxedema,¹,² thus providing valuable diagnostic clues for the internist. Whereas xanthelasmas themselves rarely represent a strictly therapeutic indication,³ patients often seek removal for cosmetic reasons.

Until approximately 2 decades ago, surgery was the only proven method for xanthelasma removal, and it remains the “classical” treatment of the lesions. The results were initially satisfactory, especially after the introduction of microsurgical techniques, but there was an ongoing search for viable alternatives because of high recurrence rates that called for repeated procedures in the delicate peri-orbital region⁴ and yielded a cumulative risk of complications such as ectropion. Chemical peeling with trichloroacetic acid is an alternative but is not readily accepted because most patients are unwilling to tolerate the application of aggressive acids close to their eyes. Therefore, the search proved to be futile until ablative laser surgery was introduced in the 1980s.⁵,⁶

Despite positive results of carbon dioxide⁵,⁷ and erbium-doped yttrium aluminum garnet⁸ laser treatments, several major shortcomings of ablative laser surgery necessitated ongoing research for alternatives.

1. The procedure is painful and thus requires some form of anesthesia.

*Laserklinik Karlsruhe, Karlsruhe, Germany; †Department of Dermatology, University of Heidelberg, Heidelberg, Germany

© 2010 by the American Society for Dermatologic Surgery, Inc. • Published by Wiley Periodicals, Inc. • ISSN: 1076-0512 • Dermatol Surg 2010;36:1–8 • DOI: 10.1111/j.1524-4725.2010.01514.x
2. Ablative laser treatment causes an open wound, which makes the patient unable to work for several days and requires meticulous wound care.

3. Because the risk of recurrence remains the same after surgical removal, it must also be assumed that procedures will have to be repeated. The risk of scarring that occurs when the subcutis is erroneously involved may be low in a single, meticulously performed procedure but accumulates over time. If scars form in the treatment area, the procedure per se is rendered useless, because cosmetic concerns are what brought the patient to the laser surgeon’s office in the first place.

4. In cases of droopy lids (blepharochalasis), tissue ablation and the thermal effect leading to collagen shrinkage cause involuntary, uncontrollable, and asymmetric retractions (Figure 1).

The perspective of nonablative laser treatment of xanthelasma is intriguing, but however promising the results may be, treatment protocols and evaluation methods are inconsistent, and evidence is too weak to draw valid conclusions and to extrapolate therapy recommendations. Therefore, we conducted a systematic trial of pulsed dye laser (PDL) treatment of xanthelasmas, using methods that were employed previously so as to facilitate a comparison of the results.

**Materials and Methods**

**Patients**

Twenty consecutive female Caucasian patients (aged 38–68, mean 53.0 ± 8.5) with *xanthelasma palpebrarum* (elevation of ≤1 mm above skin level) were enrolled in the study. To ensure patient safety, the patients were not admitted if any of the following criteria were present: Fitzpatrick skin type IV to VI; marked “dark circles” (peri-orbital hyperpigmentation); sun exposure, tanning beds or tanning creams within 4 weeks before treatment; laser surgery within 12 weeks before treatment; hypersensitivity to light; photosensitizing medication (such as tetracycline or gold); anticoagulants; seizure disorders triggered by light; active localized infection; pregnancy; unreasonable treatment expectations; and inability or unwillingness to meet the treatment and follow-up criteria.

Patients were given detailed information before the first treatment, including the risks, benefits, potential complications, and alternative treatments, and written informed consent to participate was obtained. The study complied with the Declaration of Helsinki and good clinical practice principles.

![Figure 1. Xanthelasma palpebrarum on the right upper eyelid of a 56-year-old female patient before treatment (top); note the pronounced droopy eyelids. Clinical appearance 2 months after a single carbon dioxide laser treatment (middle and bottom). The lesion was completely removed, but the laser-induced retractions and defects in the tissue lead to a cosmetically unacceptable result. The arrow points at the so-called “curtain sign” (bottom). The patient was referred to a plastic surgeon for blepharoplasty.](image)
**Treatment Protocol**

Patients underwent up to five treatment sessions (average 3.9 ± 1.0) with a PDL (V-Star, Cynosure Inc., Westford, MA) at intervals of 2 to 3 weeks. All treatments were performed without topical or systemic anesthesia or sedation. A cold-air cooling device was used to enhance patient comfort and epidermal protection (Cryo 5 set at level 4, Zimmer Medizin Systeme GmbH, Neu-Ulm, Germany). The treatment parameters were as follows: wavelength, 585 nm; energy fluence, 7 J/cm²; pulse duration, 0.5 ms; spot size, 10 mm; number of passes, 2. Pulses were delivered in a minimally overlapping manner, taking special care to avoid pulse stacking. To ensure consistency, all laser treatments were performed by the same physician (SK), who did not participate in the evaluation.

**Safety**

The patients’ eyes were protected by shells placed in contact with the eyeball. The ocular conjunctiva was anesthetized using oxybuprocaine hydrochloride anesthetic eye drops (Conjuncain EDO, Bausch & Lomb, Berlin, Germany) and protected using carbomer gel (Vidisic, Bausch & Lomb) before placing the shell.

After each session, the treated area was cooled with ice packs for 10 minutes. All patients were instructed about the importance of not picking or scratching at treated sites. If crusting occurred, the patients were advised to apply an antibiotic ointment (Flammazine, Emra-Med Arzneimittel, Trittau, Germany) three times a day until the crusts fell off. They were informed about proper sun protection and the use of broad-spectrum sunscreens of their choice (during the trial and for at least 4 weeks after the final treatment session).

**Evaluation**

**Clearance:** Before the first treatment, patients’ serum lipid concentrations (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides) were determined. All photographic documentation (en face and 45° oblique) was performed using the same digital camera (EOS 350 D with Macro Lens EF-S 60 mm f/2.8 USM, Canon, Inc., Tokyo, Japan) set at a fixed distance from the patient’s face. A lens-mounted ring flash (Macro Ring Lite MR-14EX, Canon, Inc.) ensured even illumination of all parts of the face and the ability to examine subjects under controlled lighting.

Before each treatment and 4 weeks after the final session, photographic documentation was repeated.

Two independent dermatologists compared the total xanthelasma area in the follow-up photographic sets to the first set and rated the reduction of the lesion area in four categories:

- No clearance (<25% of the xanthelasma area(s) cleared);
- Moderate clearance (25–50% cleared);
- Good clearance (51–75% cleared);
- Excellent clearance (≥75% cleared).

Photos were evaluated in a blinded fashion (i.e., the photographs were mixed intra-individually, and the examiners were unaware of whether the photographs were pre- or postoperative).

**Patient Satisfaction:** Upon final examination, patients were asked to rate their overall satisfaction based on a verbal rating scale according to the following questions:

- “How satisfied are you with the result of the treatment?” (1 = not at all to 5 = very satisfied)
- “Would you undergo the treatment again or recommend it to others?” (1 = definitely not to 5 = definitely)

**Side Effects:** The investigator (SK) and the patients recorded the presence or absence of potential side effects (hyperpigmentation, hypopigmentation, blisters, crusts, weeping, drainage, atrophy, scars, and ectropion) and concomitant skin reactions (swelling, purpura).
Statistical Analysis

All data were analyzed using the SPSS/PC+ software (version 12.0 for Windows, SPSS, Inc., Chicago, IL) employing nonparametric tests (Wilcoxon signed rank test, Friedman test, Spearman rank correlation).

The significance level was set to \( p < .05 \). Descriptive statistics were also calculated (mean, standard deviation, median, minimum, maximum, numbers, percentage).

Interrater reliability was assessed as a joint probability of agreement and by employing Cohen’s weighted kappa as a measure of conformity of ratings.

Results

Clearance

The total number of treated xanthelasmas was 38 (1–4 per patient), and the majority involved the upper lid (Table 1). Eighteen lesions were 5 to 10 mm in diameter, and 20 were 10 to 20 mm in diameter.

The final examination typically indicated good clearance, and only a few lesions did not respond to the therapy at all (Figure 2). Approximately two-thirds of the lesions showed clearance greater than 50%, and one-quarter had excellent clearance (\( > 75\% \)) (e.g., see Figure 3). Clearance rate did not depend on the size of the skin lesions (data not shown).

Three patients were lost to follow-up after the third treatment session; two of these patients had had excellent clearance of their xanthelasmas upon the last examination, pointing to satisfaction as the reason for dropping out.

Improvement Between Follow-Up Examinations

Whereas improvement after the first and second session was slight and statistically not significant, the

![Figure 2. Rate of clearance (depending on the examiner).](image-url)
third and fourth treatment each showed a significant improvement over the previous examination, and so did the fifth in the patients who received it (n = 6; with a total of 11 lesions) (Table 2). In those patients, the last session yielded remarkable improvement, by almost an entire level on average, and the statistical significance makes this result all the more impressive, despite the fact that only 11 lesions were treated.

**Interrater Reliability**

Interrater reliability was excellent. The joint probability of agreement was between 76.5% and 95.2% (typically ~90%), and Cohen’s weighted kappa was between 0.676 and 0.898 (Table 3). No site was assessed with a difference of more than one level. Most discrepancies occurred between no response and moderate; lesions with good or excellent response were classified almost unanimously.

**Correlation with Systemic Lipid Concentrations**

There was no correlation between systemic lipid concentrations and treatment response.

**Patient Satisfaction**

Patient satisfaction was generally high (Table 4), and only one patient expressed profound dissatisfaction.

---

**Table 2. Average Clearance Depending on Time and Examiner (Significance in Comparison with the Previous Examination; Tied p-Values)**

<table>
<thead>
<tr>
<th>Time</th>
<th>Examiner 1</th>
<th>Examiner 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± Standard Deviation, p-value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After first session</td>
<td>1.00 ± 0.69, n/a</td>
<td>0.89 ± 0.68, n/a</td>
</tr>
<tr>
<td>After second session</td>
<td>1.06 ± 0.75, 0.08</td>
<td>0.94 ± 0.66, 0.046</td>
</tr>
<tr>
<td>After third session</td>
<td>1.33 ± 0.91, 0.02</td>
<td>1.33 ± 0.86, 0.002</td>
</tr>
<tr>
<td>After fourth session</td>
<td>1.56 ± 1.00, 0.01</td>
<td>1.75 ± 0.94, 0.008</td>
</tr>
<tr>
<td>After fifth session (when performed)</td>
<td>2.45 ± 0.52, 0.046</td>
<td>2.36 ± 0.67, 0.046</td>
</tr>
<tr>
<td>Upon final examination</td>
<td>1.74 ± 1.00, n/a</td>
<td>1.86 ± 0.92, n/a</td>
</tr>
</tbody>
</table>

No clearance = 0, moderate clearance = 1, good clearance = 2, excellent clearance = 3. n/a, not applicable.

**Table 3. Interrater Reliability**

<table>
<thead>
<tr>
<th>Time</th>
<th>Joint probability of agreement (%)</th>
<th>Cohen’s weighted kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td>After first session</td>
<td>89.9</td>
<td>0.839</td>
</tr>
<tr>
<td>After second session</td>
<td>76.5</td>
<td>0.676</td>
</tr>
<tr>
<td>After third session</td>
<td>95.2</td>
<td>0.898</td>
</tr>
<tr>
<td>After fourth session</td>
<td>87.5</td>
<td>0.877</td>
</tr>
<tr>
<td>After fifth session (when performed)</td>
<td>90.9</td>
<td>0.845</td>
</tr>
<tr>
<td>Upon final examination</td>
<td>91.2</td>
<td>0.867</td>
</tr>
</tbody>
</table>
### Side Effects

Treatment-induced purpura (38/38 lesions) typically lasted for 10 to 12 days, and swelling (38/38 lesions) cleared in 2 to 5 days. There were no major side effects such as blisters, crusts, atrophy, scars, or ectropion. No patient reported drainage or weeping from the treated sites. Hyperpigmentation occurred in three of 38 lesions (7.9%) and was still present at the end of the final 4-week follow-up. Both patients were skin type II and were treated with broad-spectrum sunscreen.

### Discussion

To our knowledge, this is the first systematic trial of treating xanthelasma palpebrarum with PDL. Previously, only a case report was published, and it showed encouraging findings. In the present study, PDL treatment resulted in interim clearance rates greater than 50% in approximately two-thirds of the lesions without major side effects. The patients’ own assessment of the treatment outcome reflected the positive results.

Selective photothermolysis of xanthelasma content in the strict sense of the term has not yielded convincing and conclusive results. In a previous study, we failed to reproduce positive findings with a Q-switched 1,064-nm neodymium-doped yttrium aluminum garnet laser published by Fusade. A morphological feature of xanthelasma is that the lipid-laden histiocytes are tightly attached to the walls of small hyperpermeable vessels. Vascular-specific lasers may be able to induce coagulation within those vessels in the upper dermis, destroying the lipid-laden cells and preventing the leakage of lipid compounds into the surrounding tissue. Studies based on this principle have shown promising results and indicated that long-pulse treatment might turn out to be a viable alternative to ablative laser surgery. The positive results of the present trial reinforce this hypothesis. We would consider it promising to verify this mechanism using histological and electron microscope examination of tissue samples after the first few treatment sessions. At present, this information is available only for the argon laser, which is of limited value considering its inconclusive efficacy.

For the time being, it is impossible to draft valid recommendations for a concrete evidence-based therapeutic procedure because only a few trials with a variety of different methods have been published. The wavelength, the number of sessions, and the pulse duration are the main variables. For example, the patient presented by Schönemark and Raulin was treated five times (wavelength, 585 nm; pulse duration, 0.35–0.45 ms; spot size, 5 mm; number of passes, not declared). In the present study, we also observed the most pronounced effect after five sessions (wavelength, 585 nm; pulse duration, 0.5 ms; spot size, 10 mm; number of passes, 2), suggesting that further clinical clearance of lesions might be achieved given a sufficient number of additional treatments. In contrast, Berger and coworkers published a study in which the treatment was repeated only once or twice at 4- to 6-week intervals (wavelength, 532 nm; energy fluence, 9 J/cm²; pulse duration, 10 ms; spot size, 3 mm; number of passes, 2–3). Clearance was determined using a patient questionnaire and considered “satisfactory from an esthetic point of view” in all but two

### TABLE 4. Patients’ Assessment of Treatment Outcome

<table>
<thead>
<tr>
<th>Rating</th>
<th>How satisfied are you with the treatment outcome?</th>
<th>Would you undergo the treatment again or recommend it to others?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, n (%)</td>
<td>1 (5.0)</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>2, n (%)</td>
<td>2 (10.0)</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>3, n (%)</td>
<td>3 (15.0)</td>
<td>3 (15.0)</td>
</tr>
<tr>
<td>4, n (%)</td>
<td>8 (40.0)</td>
<td>7 (35.0)</td>
</tr>
<tr>
<td>5, n (%)</td>
<td>6 (30.0)</td>
<td>8 (40.0)</td>
</tr>
<tr>
<td>Average ± standard deviation</td>
<td>3.8 ± 1.1</td>
<td>4.0 ± 1.1</td>
</tr>
</tbody>
</table>

*Range from not satisfied at all (1) to very satisfied (5).

†Range from definitely not (1) to definitely (5).
patients, leaving a wide area for interpretation and making it impossible to reproduce in independent studies, although it is likely that additional sessions would have continued to improve the clinical appearance in those patients. Furthermore, the extent to which the longer pulse duration in Berger’s study is responsible for the alleged difference in the number of sessions remains unresolved. Current evidence suggests that the microvessels surrounding the lipid-laden histiocytes are the main target of treatment, arguing for shorter pulse duration, leading to rapid heating within those small vessels. Eventually, we would encourage a split-face trial to allow a direct comparison of both laser devices, but apart from the aforementioned theoretical considerations, the PDL’s greater penetration depth and its larger spot size make it a better alternative. A larger spot size in particular permits faster and more effective treatment in dermatologic applications.

Conclusions

Based on our experience and in keeping with the limited amount of available literature, PDL therapy is probably the most promising method for plain xanthelasmas in terms of achieving good clearance and avoiding major side effects. The advantages of this method are the option of repeating the application in cases of recurrence, easy handling in the delicate peri-orbital area, forgoing local and systemic anesthetics, and the low risk of scarring (even in widespread cases). It is advisable to begin treatment as soon as the condition is diagnosed because of the limited penetration depth of this laser device. Also, it might be promising to combine ablative and nonablative laser surgery when attempting to remove tuberous lesions. The deep penetration that incurs the risk of subcutis damage and subsequent scar formation can theoretically be avoided, because remnants of lesions after a carbon dioxide or erbium-doped yttrium aluminum garnet laser session can subsequently be treated with the PDL. The latter has been proven to be effective in the prevention\(^{17}\) and treatment\(^{18,19}\) of scars, further emphasizing the potential benefit of such a combined approach. Finally, we should investigate whether subpurpuric treatment parameters reducing the morbidity rate (purpura) are as effective as purpuric ones.

Acknowledgments

We would like to thank Drs. Laurenz Schmitt and Gudrun Pfirrmann for their excellent technical support during the treatment and evaluation phase of this trial.

References


Address correspondence and reprint requests to: Syrus Karsai, MD, DALM, Laserklinik Karlsruhe, Kaiserstr. 104, DE-76133 Karlsruhe, Germany, or e-mail: info@raulin.de