Is Q-Switched Neodymium-Doped Yttrium Aluminium Garnet Laser an Effective Approach to Treat *Xanthelasma Palpebrarum*? Results from a Clinical Study of 76 Cases

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BACKGROUND Treating *xanthelasma palpebrarum* may prove difficult because of its delicate location on the eyelid. Various forms of nonablative laser techniques have been examined, and Q-switched neodymium-doped yttrium aluminium garnet (Nd:YAG) laser therapy has shown promising preliminary results.

OBJECTIVES To determine the efficacy of Q-switched Nd:YAG laser treatment for xanthelasma removal.

MATERIALS AND METHODS Thirty-seven consecutive patients with 76 lesions received two treatment sessions with a Q-switched Nd:YAG laser without local anesthesia (6 J/cm^2 [1,064 nm] or 2 J/cm^2 [532 nm], 4-mm spot size, 2–3 passes). Photographs were taken before each treatment session and 4 weeks after the second treatment. Two independent examiners rated clearance in four groups (none [$<$25% cleared], moderate [25–50%], good [51–75%], and excellent [$>$75%]).

RESULTS Only two-thirds of the patients completed the entire course of the study; disappointing early results were the main reason for dropping out. The majority of treated lesions (70% or 75%, depending on the examiner) showed no clearance. Plasma low-density lipoprotein cholesterol levels displayed some influence on treatment results but not enough to facilitate stratification of patients.

CONCLUSION Q-switched Nd:YAG (532 nm and 1,064 nm) laser treatment of xanthelasma cannot be recommended.

The authors have indicated no significant interest with commercial supporters.

Xanthelasma palpebrarum is the most common type of xanthoma and presents as yellowish plaques on the upper and lower eyelid. Xanthelasma might be a manifestation of a systemic disorder (mainly hyperlipidemia *sui generis*, hypothyroidism, and diabetes mellitus[1,2]) and is then seen as a clinical sign rather than a disease. It can reach a size that is sufficient to obscure vision but rarely does so,[3] making a strictly medical indication for xanthelasma therapy a rarity. However, it can be disfiguring and, depending on the patient, can represent a major impairment to quality of life that requires treatment independent of the underlying condition.

Xanthelasma consists of foamy, lipid-laden histiocytes known as xanthoma cells. The lipid deposits are formed mainly as a result of excess low-density lipoprotein cholesterol (LDL-C) in plasma and consist of cholesteryl esters.[4] Nonetheless, there is no inevitable link between plasma lipid concentrations and xanthelasma occurrence; approximately half of people with the condition are normolipidemic,[5] and its prevalence in patients with familial hypercholesterolemia is only approximately 10% to 20%. Whereas a causative role of plasma lipids is certain, evidence is inconclusive when it comes to the beneficial effect of dietary or pharmacological lipid reduction.[3]

Traditionally, the mainstay of xanthelasma therapy was surgical removal followed by microsuturing the resulting defect. Reluctance to perform surgery in

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the delicate peri-ocular region and the lesions' tendency to recur[6] has led to a search for viable alternatives, but in many cases, techniques such as cryoablation, acid peeling, and electrocauterization have failed to achieve sustained results.[3]

The application of carbon dioxide and erbium-doped YAG lasers has been reported to be successful in the majority of cases,[7,8] but there is a considerable risk of scarring if the subcutis is accidentally injured. Nonablative lasers have thus been investigated as an alternative,[9–13] but the treatment parameters, outcome assessment methods, and results vary to a substantial degree.

In 2005, Berger and Kopera[9] treated 33 lesions in 14 patients with a potassium-titanyl-phosphate (KTP) laser, a neodymium-doped yttrium aluminium garnet (Nd:YAG) laser whose frequency is doubled using a KTP crystal. They applied two to three passes (wavelength, 532 nm; energy fluence, 9 J/cm^2; pulse duration, 10 ms; spot size, 3 mm) and, depending on the response, repeated the treatment once or twice with 4- to 6-week intervals in between. Clearance was determined by comparing photographs and was considered "satisfactory from an esthetic point of view" in all but two patients.

In 2008, Fusade[13] treated 38 lesions in 11 patients using a Q-switched 1,064-nm Nd:YAG laser (energy fluence, 4–8 J/cm^2; pulse duration, 5–7 ns; spot size, 2 mm). The results are presented per patient rather than per lesion; in six patients it was rated excellent (>75% clearance), in two patients good (50–75%), and in the remaining three moderate (50–75%).

Because the possible advantages of Q-switched Nd:YAG laser treatment of xanthelasma are intriguing, we evaluated the benefits of a recent study[13] based on a larger sample of patients employing both wavelengths (532 and 1,064 nm).

Materials and Methods

Patients

Thirty-seven consecutive Caucasian patients (11 men, 26 women, aged 32–75, mean age 54.4 $\pm$ 10.3) were enrolled in the study. To be eligible, patients had to fulfill the following criteria:

- Diagnosis of *xanthelasma palpebrarum* with an elevation of 1 mm or less above skin level
- Fitzpatrick skin type I to III
- No treatment (including laser therapy) within 12 weeks before being enrolled in the study
- Absence of "dark circles" (peri-orbital hyperpigmentation) to prevent interference with the melanin-sensitive 532-nm wavelength

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

Treatment

The lesions were treated using a Q-switched Nd:YAG laser (Affinity, Cynosure, Westford, MA) without local anesthesia. Depending on the site of the lesion, the patient's eyes were appropriately covered using metal scleral eye shields before treatment (similar to the method described by Fusade[13]).

Fifteen patients with bilateral symmetrical lesions randomly received 532 nm treatment on one side and 1,064 nm treatment on the other; in the remaining 22 patients, all lesions were treated with 1,064 nm. The treatment settings were as follows:

- 1,064 nm wavelength, 6 J/cm^2 energy fluence, 5 Hz frequency, 6-ns pulse duration, 4-mm spot size, two to three passes (no stacking) until pin-point bleeding occurred
- 532 nm wavelength, 2 J/cm^2 energy fluence, 5 Hz frequency, 6-ns pulse duration, 4-mm spot size,

two to three passes (no stacking) until whitening occurred

After treatment, the lesions were covered using an antibiotic ointment (Flammazine, Emra-Med Arzneimittel, Trittau, Germany) for 3 days. The patients were advised to avoid sun exposure and tanning booths during the trial and for at least 4 weeks after the final treatment session.

Patients received two treatment sessions with 4 weeks in between.

Examinations

Before the first treatment, patients' fasting serum lipid concentrations (total cholesterol, high-density lipoprotein cholesterol, LDL-C, triglycerides) were determined, and photographs of the lesions were taken.

Before the second treatment session (after 4 weeks) and another 4 weeks later, photographic documentation was repeated.

All photographic documentation was performed using the same 60-mm camera (EOS 350 D, Canon Inc., Tokyo, Japan) using a fixed distance and fixed angles between the camera and the patients' faces. Flash lamps placed in fixed positions to the camera ensured even illumination of all parts of the face and the ability to examine subjects under controlled lighting.

Two independent, experienced dermatologists compared the second and third set of photographs with the first set in terms of improvement 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)

To enhance scientific validity, the examiners did not know which were the before and after pictures.

Spectroscopic Analysis

Optical transmission ($T_{(lambda)}$) of a LDL-C specimen (10 mg/mL in chloroform; Sigma-Aldrich, Taufkirchen, Germany) was determined using a Cary spectrometer (Varian, Palo Alto, CA) covering the visible and infrared range ($\lambda = 400–2{,}400$ nm). Optical absorption ($A_{(lambda)}$) was calculated using the equation:

$$A_{(lambda)} = -\log(T)_{(lambda)}$$

Statistical Data Evaluation

The chi-square test and analysis of variance were used to evaluate data.

The interrater reliability of the panel of dermatologists who evaluated photographs of participants was assessed as a joint probability of agreement and by employing Cohen's weighted kappa as a measure of conformity of ratings.

Results

Global Results

Overall, 76 lesions were treated at least once, with a clear domination of the upper lid and a rather marked preference for the left side of the face (Table 1).

Fifty-seven lesions (75.0%) were treated with a wavelength of 1,064 nm, and the remaining 19 sites (25.0%) received 532 nm treatment.

Two patients with one lesion each dropped out of the study before the second treatment, and four patients (totaling 7 lesions) were not examined at least once. Another 19 lesions in 11 patients were unavailable upon the second follow-up, rendering the number of courses completed per protocol 50 (65.8%). Although the withdrawal rate was substantial, this

TABLE 1. Location of Treated Lesions

	n (%)		
Eyelid	*Left*	*Right*	*Sum of Upper and Lower*
Upper	32 (42.1)	17 (22.4)	49 (64.5)
Lower	15 (19.7)	12 (15.8)	27 (35.5)
Sum of both sides	47 (61.8)	29 (38.2)	76 (100.0)

was probably a reflection of dissatisfaction with the treatment.

Consistently throughout the visits, both examiners rated the majority of lesions as not responding to treatment (Figure 1).

Improvement Depending on the Wavelength

A breakdown of sites according to applied wavelength, examiner, and number of examinations revealed no convincing advantage of either treatment modality (Table 2). Whereas the 532-nm wavelength appeared as if it might show some advantage at both examinations, the small total number of patients completing follow-up after this treatment substantially attenuated this.

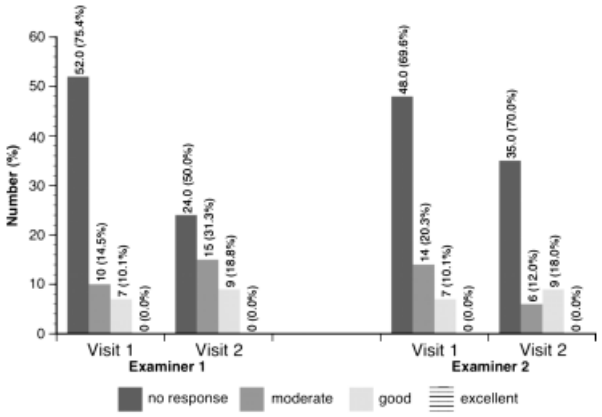

Figure 1. Rate of clearance (depending on time and examiner).

Improvement Between Follow-Up Examinations

The vast majority of sites with complete follow-up showed no improvement after the second treatment session; examiner 1 estimated the proportion of unchanged lesions to be 75.0% and examiner 2, 90.0% (Table 3). The 532- and 1,064-nm wavelengths showed no difference with respect to improvement between examinations.

Interrater Reliability

Interrater reliability (joint probability of agreement) was 76.8% at the first visit and 68.8% at the second. Cohen's kappa was 0.62 (examiner 1) and 0.64 (examiner 2), indicating substantial agreement. The ratings of examiner 1 at the first examination were somewhat higher than the respective ratings of examiner 2, whereas the opposite was true at the second examination. In only one lesion was the difference in classification more than one degree (Table 4).

Correlation with Systemic Lipid Concentrations

There was a clear statistically significant correlation between clinical improvement and serum LDL-C concentrations; patients with lower LDL-C concentrations were consistently more likely to have a good response than a moderate and no response (Figure 2), but this did not facilitate stratification of patients for treatment, because even in the lowest LDL-C stratum (< 100 mg/dL) nonresponders represented the largest proportion of the sample.

Spectroscopic Analysis of LDL-C

A sample of LDL-C showed chromophoric absorption peaks of different amplitudes at approximately 1,700, 2,100, 2,300, and 2,400 nm. No peaks were registered near the Nd:YAG laser's operating wavelengths (532 and 1,064 nm) (Figure 3).

Side Effects

The treatments were all well tolerated without the use of local anesthesia.

TABLE 2. Rate of Clearance (Depending on Wavelength, Examiner, and Number of Examinations)

	Clearance n (%)				
Condition, nm	*None*	*Moderate*	*Good*	*Excellent*	*Lost to Follow-Up*
532					
Visit 1					
Examiner 1	13 (76.5)	1 (5.9)	3 (17.6)	0	2 (10.5)
Examiner 2	13 (76.5)	1 (5.9)	3 (17.6)	0	2 (10.5)
Visit 2					
Examiner 1	3 (27.3)	4 (36.4)	4 (36.4)	0	8 (42.1)
Examiner 2	7 (58.3)	1 (8.3)	4 (33.3)	0	7 (36.8)
1,064					
Visit 1					
Examiner 1	39 (75.0)	9 (17.3)	4 (7.7)	0	5 (8.8)
Examiner 2	35 (67.3)	13 (25.0)	4 (7.7)	0	5 (8.8)
Visit 2					
Examiner 1	21 (56.8)	11 (29.4)	5 (13.5)	0	20 (35.1)
Examiner 2	28 (73.7)	5 (13.2)	5 (13.2)	0	14 (33.3)

Treatment-induced pinpoint bleeding and crusting typically lasted for 7 to 10 days, and swelling cleared in 2 to 5 days. There were no major side effects such as atrophy, scars, blisters, hypopigmentation, or hyperpigmentation. No patients reported drainage or weeping from the treated sites.

Discussion

This study includes the highest number of treated patients and lesions reported in the literature to date, and the results are sobering. It shows the limits of the 532- and 1,064-nm Q-switched Nd:YAG laser in treating *xanthelasma palpebrarum*, despite the use of optimized treatment parameters (4 mm vs 2 mm spot size for greater penetration depth, 2 sessions vs 1 for greater efficacy, and no local anesthesia, which could impair penetration depth and affect laser lipolysis[14]). Moreover, these findings are in stark contrast to those published recently by Fusade.[13] If anything, the different application mode—the doubled spot size and number of sessions—should have *increased* the efficacy, possibly at the expense of yielding a higher rate of side effects. Doubling the spot size will increase the effective volume by a factor of 8; as a general rule, doubling the spot size and halving the fluence will yield an equivalent effective fluence at a given depth.[15]

Differences in sociodemographic data or plasma lipid levels, although present to some extent, also cannot explain the radically different results between our study and those published recently,[13] but a few points suggest possible reasons for the discrepancy observed between our results (or rather, the lack thereof) and those published so far.

First, by definition, it is difficult to compare published results when the authors fail to give sufficient detail on their method of measurement. For instance, Berger and Kopera[9] use the term "satisfactory from an esthetic point of view" (translated from German

TABLE 3. Change in Clearance Between Follow-Up Visits in Patients with Completed Follow-Up

	Change in Clearance n (%)				
Examiner	*2 Degrees Better*	*1 Degree Better*	*No Change*	*1 Degree Worse*	*2 Degrees Worse*
1	0	12 (25.0)	36 (75.0)	0	0
2	0	5 (10.0)	45 (90.0)	0	0

TABLE 4. Interrater Reliability

		n (%)			
		Examiner 1		*Examiner 2*	
Visit	*Reliability, %*	*+ 2 Degrees*	*+ 1 Degree*	*+ 1 Degree*	*+ 2 Degrees*
1	76.8	1 (1.4)	8 (11.6)	6 (8.7)	0
2	68.8	0	3 (6.3)	12 (25.0)	0

by the author), which leaves a rather wide area for interpretation and is impossible to reproduce in independent studies. But this is not the only reason, since our method of evaluation was specifically chosen to be similar to that employed by Fusade.[13] Nevertheless, it yielded very different—almost reciprocal—results. The most frequent finding in Fusade's study, excellent clearance of 75% or more of the lesions, did not occur at all in the present study, and vice versa. The majority of lesions in the present study, and no patient in Fusade's trial, showed no clearance. This discrepancy is striking and would require fundamental differences in study design, which we fail to recognize.

It remains unresolved whether (and to what degree) the longer pulse duration in the study by Berger and Kopera[9] is responsible for the striking difference in the results. From histological studies, we learned that typical xanthoma cells are closely attached to the wall of small hyperpermeable vessels.[16] Using long-pulsed lasers (as employed by Berger and Kopera), it might be presumed that the laser-induced coagulation of the vessels within the upper dermis leads to damage to these perivascular cells. Coagulation of the pathologically hyperpermeable vessels could conceivably have led to a block of the leakage of lipids into the tissue, preventing recurrent lesions. This concept needs to be evaluated in clinical studies of high enough statistical power.

The foundation of selective photothermolysis is based on the principle of the differential absorption behavior of tissues or substances embedded in them. The wavelength of the laser is chosen to be as close as possible to the absorption maximum of the target tissue or substance (e.g., tattoo ink) and as far as possible from that of the surrounding tissue. In vitro studies have shown that fatty tissue can be selectively targeted with laser light of 1,064 nm,[17,18] but these results refer to subcutaneous tissue containing predominantly triglycerides. The spectral analysis of

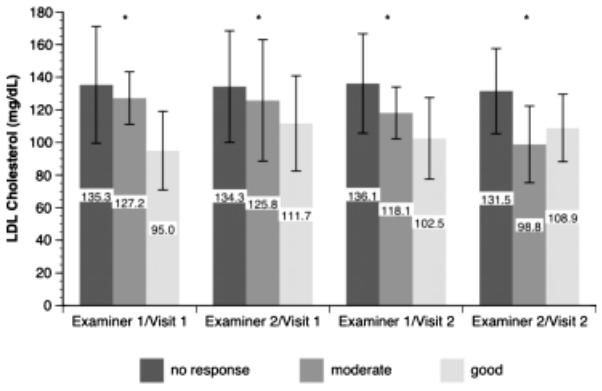

Figure 2. Serum low-density lipoprotein cholesterol levels depending on treatment response (mean ± 1 SD, $^{*}p < .001$).

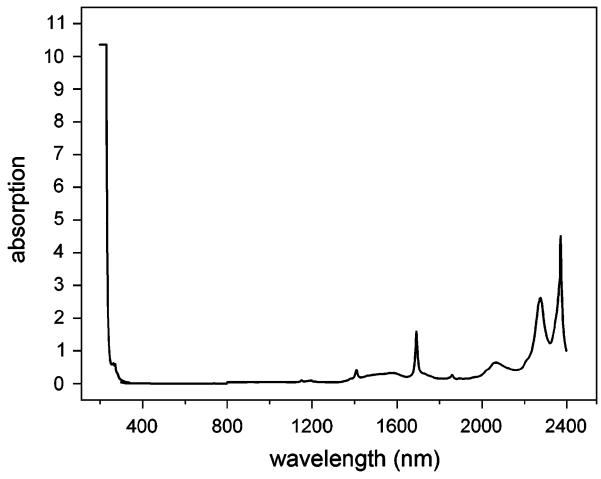

Figure 3. Low-density lipoprotein cholesterol absorption spectrum (for details, see Materials and methods).

LDL-C presented in Figure 3 may explain the lack of an effect in our observation. Although technical hurdles prevented us from analyzing the absorption behavior of actual xanthelasma content, the analysis of an LDL-C sample showed peaks that were nowhere near the wavelengths under investigation. In contrast to tattoos, on which the Q-switched Nd:YAG laser has a well-understood effect because of its specific absorption behavior, selective removal of the fatty tissue of xanthelasmas would be hard to explain from a physical point of view.

A brief review of the current literature on laser removal of xanthelasma directs the focus of discussion to a methodological issue. With some regularity, it shows the occurrence of "successful" new treatment modalities that other groups never follow up and confirm. What is known as the "file drawer problem," an established term in evidence-based medicine, may in part explain this phenomenon: Studies are most likely to be completed and published if they yield significantly positive results. Investigators trying to follow up on results like those published by Fusade[13] may have abandoned trials or decided not to submit them for publication. Indeed, the lack of an effect of the laser treatment was obvious early on in the present study, and carrying on and completing the study required a fair amount of endurance on the part of the investigators and patients (which was not always present in the latter group, as reflected by the substantial number of
patients lost to follow-up).

It is not justified to even roughly estimate the number of trials that may have been abandoned, so conclusions should be drawn exclusively from our own results and those published previously.

Conclusion

The Q-switched Nd:YAG (532 and 1,064 nm) laser treatment of *xanthelasma palpebrarum* cannot be generally recommended and should be applied with caution, if at all. In this context, it should be emphasized that laser treatment in close proximity to the patient's eyes constitutes a substantial risk. Although this study—as well as several others (e.g., [9,12,13])—shows that this treatment can be performed without any side effects, it may cause damage, especially when inexperienced laser surgeons apply it.[19,20] Our own results as such would hardly warrant further studies, but this conclusion will not be unanimous. The fact that our study does not substantiate the positive results recently reported is not an indictment of nonablative laser therapy for xanthelasma in general and does not necessarily exclude the possible role of lasers in laser lipolysis per se, but it suggests that additional well-designed studies are needed before the Q-switched Nd:YAG laser becomes a part of xanthelasma therapy. In the greater scheme of things, the modality should be applied strictly in study situations of high methodological quality. The goal should be to clarify controversial concerns that require comparability with the success criteria of trials that have already been published.

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