Comparison of the Q-switched Alexandrite (755 nm) and Q-switched Nd:YAG (1064 nm) Lasers in the Treatment of Benign Melanocytic Nevi

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BACKGROUND. A variety of pigmented lesions have been shown to be effectively treated with several pigment-specific laser systems currently available. There has been recent evidence to indicate that they may also be useful in the treatment of melanocytic nevi.

OBJECTIVE. To compare the clinical and histologic effects of the Q-switched (QS) alexandrite (755 nm) and Nd:YAG (1064 nm) lasers in the treatment of melanocytic nevi.

METHODS. Eighteen patients received three QS alexandrite and Nd:YAG laser treatments to either half of a large nevus or to two small adjacent nevi. Tissue biopsies were obtained for histologic examination. Degree of clinical improvement was determined by comparative photographic global assessment scores. The amount of melanin present within the nevus before and after laser irradiation was measured by reflectance spectrometry.

RESULTS. Clinical global assessment scores were significantly reduced in all QS alexandrite and QS Nd:YAG laser-treated nevi after three treatments. Melanin reflectance spectrometry scores improved after the first laser treatment only. Histologically, a significant reduction in epidermal pigmentation and melanocytes were observed following laser irradiation with either QS system.


Ever since the ruby laser was first used in the early 1960s to treat human skin, a variety of lasers have become standard means for treating various cutaneous anomalies. Endogenous pigments, such as oxyhemoglobin and melanin, can be selectively targeted and destroyed by currently available lasers. A variety of lasers emitting different wavelengths of light can target melanin due to its broad absorption spectrum. Superficial pigmented lesions, including solar lentigines and cafe-au-lait macules, can be treated by lasers emitting green light, such as the QS Nd:YAG (frequency doubled to 532 nm) and 510-nm pulsed dye lasers. Dermal melanocytic lesions, such as nevus of Ota, will not respond to green light laser irradiation due to limited tissue penetration by these short wavelengths. The QS Nd:YAG (1064 nm), QS alexandrite (755 nm), and QS ruby (694 nm) lasers, however, emit light at longer wavelengths, thereby allowing adequate dermal penetration.

The QS ruby laser has recently been shown to be effective in lightening congenital melanocytic nevi. To date, no study has examined the effect of other pigment-specific lasers in the treatment of melanocytic nevi. We report the results of a prospective trial comparing the QS alexandrite (755 nm) and QS Nd:YAG (1064 nm) lasers to treat benign melanocytic nevi. Eighteen patients with melanocytic nevi received three laser treatment sessions with both of these QS laser systems. Clinical and histologic effects of QS alexandrite and QS Nd:YAG irradiation were determined and compared.

Materials and Methods

Patient Inclusion Criteria

Patients with pigmented nevi present for at least 10 years were eligible for inclusion in the study. It was necessary for a nevus to be at least 1.5 cm in diameter or for two nevi, each greater than 7 mm in diameter, to be present. Additional criteria included uniformity in color and regularity of borders. In order to treat, nevi with pigment restricted to the epidermal junction and superficial dermis, only those patients whose nevi were flat without surface textural change relative to the surrounding normal skin were included. Patients with

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a personal or family history of melanoma were excluded. Eighteen patients (aged 2-76 years; mean age, 39.1 years) met the eligibility criteria described above. All patients were classified with skin phenotypes I-III.

**Laser Treatment Protocol**

A QS alexandrite laser with a 755-nm wavelength, 100-nsec pulse duration, and 3-mm spot size (TATULAZR; Candela Laser Corporation, Wayland, MA) was used on one-half of a large nevus (>15 mm diameter) or on one of two nevi (measuring 7-15 mm diameter) in an individual patient. A QS Nd:YAG with a 1064-nm wavelength, 20-nsec pulse duration, and 3-mm spot size (Candela Laser Corporation) was used on the contralateral half of a large nevus or on the second nevus measuring 7-15 mm in diameter. Random assignment of laser treatment was made in each study patient and patients were blinded with respect to the laser used. Both lasers were utilized at fluences of 60 J/cm²—energy densities that had been shown through pretrial experience to produce the desired degree of tissue whitening immediately upon laser impact.

Three laser treatments were delivered at 6-week intervals. No topical or intralobular anaesthesia was utilized. Confluent laser pulses were placed in a nonoverlapping pattern over the entire nevus. Immediately following treatment, a topical antibiotic ointment was applied. A protective dressing was placed over the treated region (Coverlet; Boersdorf Inc., Norwalk, CT). Patients were instructed to reapply topical antibiotic ointment and change the dressing daily for 1 week after each laser treatment. Six weeks following the third treatment (18 weeks), a final evaluation was performed.

**Photographic Analysis**

Photographs of the nevi under study were obtained immediately prior to each laser treatment (baseline, 6, and 12 weeks) and at study termination (18 weeks) using a 35-mm single reflex camera equipped with a lens mounted ring flash (Nikon Corporation, Japan). ASA 100 film (Kodachrome; Eastman Kodak Company, Rochester, NY) was used and all film was processed by a single laboratory.

**Melanin Reflectance Spectrometry (MRS)**

A hand-held reflectance spectrometer (DermaSpectrometer, Cortex Technology, Hadsund, Denmark) was used to measure the melanin content of the study nevi and the uninvolved surrounding skin. The instrument, when placed on the skin, provides an immediate digital value that corresponds to the amount of melanin in the underlying tissue. The mean of three measurements was calculated in each treatment site at each visit in order to ensure maximal accuracy.

**Histologic Evaluation**

Twenty-four punch biopsies (3 mm) were obtained for histologic examination. Nevi in cosmetically sensitive areas were not biopsied. Hematoxylin & eosin-stained formalin-fixed histologic specimens were blindly examined for quantity of epidermal and dermal melanocytes and presence of fibrosis before and after laser therapy. Epidermal pigmentation was also determined using a rating scale ranging from 1 to 3 (1 = sparse pigment, 2 = moderately dense pigment, 3 = very dense pigment).

**Clinical Statistical Analysis**

A global assessment score (GAS) was obtained by side-by-side comparison of photographs of treated nevi to reference photographs taken at baseline. Two blinded physician assessors independently assigned a numeric score on a scale of 0-10 for each nevus. The GAS was based on the percent improvement as follows: 10 represented no improvement, 9 represented 10% improvement, 8 represented 20% improvement, and so on. As such, all nevi at baseline were given a score of 10.

MRS scores were recorded as the ratio of the nevus melanin measurement to the normal skin melanin value. Ratios were calculated in all nevi before and 6 weeks after each of the three QS alexandrite- and QS Nd:YAG laser treatments.

Statistical calculations were performed using an integrated data analysis software system (StatView: Abacus Corporation, Berkeley, CA). Means for GAS and MRS were obtained at baseline and at weeks 6, 12, and 18 in the QS alexandrite- and QS Nd:YAG-treated areas. The two-tailed paired t-test was used to compare the means to baseline. The mean GAS and MRS of the QS alexandrite- and QS Nd:YAG-treated nevi obtained at the four evaluation periods were also compared with each other using a two-tailed unpaired t-test.

**Results**

**Clinical Global Assessment Scores**

Both the QS alexandrite- and QS Nd:YAG laser systems resulted in statistically significant improvement in GAS (Figure 1). A small decrease in GAS was observed in nevi after one treatment with the QS alexandrite- or QS Nd:YAG laser. The mean GAS for QS alexandrite-treated nevi decreased from 10.0 at baseline to 9.1 (P = 0.0048) after a single treatment session (week 6), whereas the QS Nd:YAG-treated nevi scores fell from 10.0 at baseline to 9.4 (P = 0.0201). There was no difference between the laser-treated groups 6 weeks after the first laser treatment.

Six weeks after the third treatment (at week 18), mean GAS scores in both laser-treated groups were dramatically reduced from baseline (Figures 2-5). The mean GAS was 4.1 (P < 0.0001) for QS alexandrite-treated nevi and was 6.8 (P < 0.0001) for those treated with the QS Nd:YAG laser. There was a statistically significant difference between the two laser-treated groups (P = 0.0035).

Side effects were observed in four patients, all of whom developed transient hyperpigmentation in both the alexandrite- and Nd:YAG-treated sites, that resolved by week 18. A faint blue-gray skin coloration was seen in both groups of nevi as the pigment cleared, representing a possible Tyndall effect of residual melanin in the skin.

**Melanin Reflectance Spectrometry**

The mean MRS scores at baseline for QS alexandrite- and QS Nd:YAG-treated nevi were 1.41 and 1.44, re-
spectively (Figure 6). An unpaired t-test showed no significant difference at baseline between these two groups. By week 6 (after one treatment), both laser-treated nevi groups improved from baseline. Specifically, the mean MRS of the QS alexandrite-treated nevi was reduced to 1.27 ($P = 0.0172$) and that of the QS Nd:YAG-treated group was 1.30 ($P = 0.0045$). Unlike the GAS, the mean MRS scores did not continue to improve after the first treatment. Furthermore, an unpaired t-test revealed that the QS alexandrite mean MRS was not significantly different from the Nd:YAG mean at any of the treatment visits. These unexpected observations could be due to reduced accuracy of the melanin spectrometer as nevi lightened. Alternatively, the blue-gray discoloration observed in the fading nevi may have led to a miscalculation by the spectrometer. Subjective clinical assessment error seems unlikely to have been responsible since MRS scores were largely unchanged after the first treatment, even in those nevi that had dramatic clinical improvement.

Figure 2. Two-year-old boy with a congenital melanocytic nevus.

Figure 3. Six weeks after three treatments with the QS alexandrite laser (left half of nevus) and QS Nd:YAG laser (right half).
Histology

Baseline tissue biopsies revealed histologic findings consistent with compound melanocytic nevi in all but one sample, which showed a junctional melanocytic nevus (Figure 7). There was no evidence of dysplasia in any of the specimens. The mean baseline epidermal pigmentation score was 1.91 (n = 11). All baseline specimens showed moderate junctional melanocytic hyperplasia composed of discreet, well-formed nests. All compound melanocytic nevi contained orderly nests, cords, and strands of benign nevomelanocytes. There was no fibrosis in any of the baseline specimens.

Histologic evaluation of 13 postoperative specimens revealed a significant reduction in the epidermal pigmentation score following QS laser irradiation, with a mean of 1.31 (P = 0.001). The number of intraepidermal melanocytes was reduced, with markedly diminished junctional nests and a slightly decreased dermal density of nevomelanocytes (Figure 8). Heavily pigmented dermal melanophages and mild dermal fibrosis were observed. There was no appreciable difference between the two laser-treated groups in terms of epidermal pigmentation, number of melanocytes, or fibrosis.

Discussion

The QS alexandrite (755 nm) and Nd:YAG (1064 nm) lasers are designed to treat pigmented cutaneous lesions. These lasers follow the basic principles of selective photothermolysis, delivering short bursts of high-intensity light to targeted tissue in a manner that avoids heat accumulation and thermal injury in adjacent normal skin. The longer wavelengths of these pigment-specific lasers can penetrate to the reticular dermis, thereby permitting destruction of such deep pigmented disorders as nevus of Ota.

This study demonstrates and compares the effectiveness of the QS alexandrite and QS Nd:YAG lasers in the treatment of melanocytic nevi. Only those patients who had nevi present for at least 10 years were enrolled in the study. In addition, the nevi were required to be flat with uniform pigmentation. Histologic evaluation confirmed benign nevomelanocytes restricted to the superficial dermis in all biopsied specimens.

A single treatment using the QS alexandrite or QS Nd:YAG laser at 6.0 J/cm² (spot size, 3 mm) resulted in slight, but statistically significant, improvement in mean GAS and MRS scores. After three laser treatments, dramatic clinical lightening was noted in both groups of laser-treated nevi. The QS alexandrite laser produced better global assessment scores compared with the QS Nd:YAG after three laser treatments. The fact that the MRS scores did not improve commensurately with GAS after the second and third treatments may be explained by possible spectrometer inaccuracy as the nevi faded with more blue-gray discolouration. Evaluator error of GAS is a possible, but less likely, explanation because nevi that were almost totally clear clinically also did not display improvement in their MRS scores.

Histologic evaluation showed similar changes in nevi following irradiation by either QS laser. Decreased numbers of epidermal and dermal melanocytes, as well as an overall reduction in epidermal pigment, are the likely histologic counterparts to the dramatic clinical lightening observed. While slight fibrosis was noted histologically, there was no textural change seen clinically. The pale blue-gray color observed in the treated nevi could represent a Tyndall effect created by the reduction in superficial melanin and melanocytes.

The fluence of 6.0 J/cm² was chosen for standardization of each treatment based on extensive pretrial expe-
Figure 6. Melanin reflectance spectrometry scores expressed as a ratio of the nevus melanin to the surrounding normal skin.

Figure 7. Baseline histopathology of a compound melanocytic nevus before laser treatment shows epidermal pigment and benign nests of melanocytes at the dermal-epidermal junction and in the dermis.

Figure 8. After three treatments with the QS Nd:YAG laser, minimal residual epidermal pigmentation is present with markedly diminished melanocytes at the dermal-epidermal junction and in the dermis.
play on the process of malignant transformation. Some have proffered that reducing the overall pigmentation burden could possibly result in a lower incidence of malignant transformation. In the same vein, there has not been a case report to date of malignant transformation in a nevus of Ota after laser irradiation. Equally encouraging in terms of safety is that countless melanocytic nevi have, no doubt, been inadvertently lasered during treatments for other conditions, but malignant melanoma has not been reported in regions previously exposed to any of the pigment-specific lasers. These arguments notwithstanding, most of the laser-treated nevi in our study were excised for histologic evaluation. Those patients who refused excision of their nevi for cosmetic or other reasons will continue to receive regular dermatologic evaluations.

The cosmetic benefit of Q-switched laser irradiation surpasses the clinical effect of more traditional treatment, namely, excision. Scarring is unusual in patients treated with the pigment-specific lasers. We have shown that considerable lightening of longstanding melanocytic nevi can be achieved after three laser treatments. This study was limited to three laser treatments based on anecdotal pretrial experience. Judging from the improvement seen after the third treatment, it is probable that additional treatment would prove beneficial. What remains to be seen is whether the observed changes in nevi treated with pigment-specific pulsed lasers are permanent.

Note: Twelve-month follow-up of 12 of the 18 patients in this study revealed no evidence of lesional recurrence or pigment darkening.

References

Commentary
Selective photothermolysis, a concept described by Parrish and Anderson, describes the selective use of a particular wavelength of laser energy to destroy a particular chromophore. In the treatment of vascular lesions, lasers emitting either green or yellow light are absorbed by one of the two absorption peaks of hemoglobin. The melanin absorption curve is distinctly different than that of hemoglobin: it is broad based.

Melanin, contained within melanosomes, absorbs laser light throughout the visible light spectrum and into the near infrared spectrum. Because of this broad melanin absorption, lasers emitting any color of light will impact on pigmented lesions. The difference between pigmented lesion lasers has more to do with the depth of laser penetration than absorption by melanin. The longer the wavelength the deeper the penetration. Thus, green light lasers will improve epidermal pigmented lesions such as epithelides and solar lentigines. However, these lasers do not penetrate deep enough to effect dermal pigmented lesions. Red and near infrared lasers, such as the Q-switched ruby, Alexandrite, and Nd:YAG lasers, have all been shown to be effective in the treatment of dermal pigmented lesions such as nevus of Ota. Thus, it is not surprising that Rosenbach et al have shown the effectiveness of the Q-switched Alexandrite lasers in the treatment of benign melanocytic nevi, lesions often with dermal melanocytes.

Although these lasers clearly improve the appearance of dermal pigmented lesions, two questions continue to nag cutaneous laser surgeons. 1) Are the current lasers the best for the treatment of pigmented lesions? 2) What is the effect of visible and near infrared lasers on melanocytes?
Although the currently available pigmented lasers are highly effective in the removal of epidermal pigmented lesions, they only improve many dermal pigmented lesions. The Japanese have extensive experience with non-Q-switched ruby lasers. These longer pulsed lasers appear to be more effective than their Q-switched cousins in the treatment of dermal pigmented lesions. Thus far, there is minimal U.S. experience with these lasers.

Q-switched ruby, alexandrite, and Nd:YAG lasers can destroy some of the melanocytes in nevus of Ota and other nevi. What is the effect of these lasers on melanocytes? Can they convert normal melanocytes into atypical melanocytes? There is no evidence to support this concern. Green light lasers, such as the argon laser, have been used to treat pigmented lesions for thirty-five years. There has never been any evidence of a laser-treated pigmented lesion "converting" typical melanocytes to atypical melanocytes. If this is to happen, the incidence must be extremely rare.

The answer to the above questions will only be answered by continued research and continued documentation of the effect of cutaneous lasers on pigmented lesions.

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