Treatment of Refractory Melasma in Asians With the Picosecond Alexandrite Laser

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BACKGROUND/OBJECTIVES The picosecond Alexandrite laser was studied in our practice with the diffractive lens array and the flat optic to treat melasma.

METHODS AND MATERIALS Sixty patients with melasma were treated in a prospective investigation with the picosecond Alexandrite laser. Nineteen patients were treated with the flat optic and 41 patients were treated with the diffractive lens array. Treatments were performed with 1 pass at 2-week intervals for 6 treatments. The Melasma Severity Index (MSI) was used to evaluate the patients before treatment and 3 and 6 months after the final treatment session.

RESULTS At 6 months after the last treatment, there was an 18.5% difference between the groups with a 75.7% improvement in the MSI in patients with the diffractive lens array and a 57.2% improvement in the MSI score in patients with the flat optic. At 6 months, there was recurrence of melasma in 5% of the cases with no hyperpigmentation with the diffractive optic in contrast to recurrence in 16% of the cases in the flat optic group and a transient macular hyperpigmentation in 21% of the cases.

CONCLUSION This investigation highlights the utility of a picosecond Alexandrite laser with a flat and diffractive lens to successfully treat a large percentage of Asian patients in a sunny climate.

E. Tanghetti is a consultant, speaker, clinical studies for Hologic. The remaining author has indicated no significant interest with commercial supporters.

The treatment of melasma often confounds and frustrates both patients and the provider. Hydroquinone is the most common topical agent used throughout the world. Prolonged application or the use of high concentrations of this drug has been only marginally helpful and has resulted in local irritation or in some cases paradoxical hyperpigmentation, ochronosis. Other alternative treatments include chemical peels, intense pulsed light, copper bromide laser, and fractional nonablative devices. These devices have often resulted in temporary mild improvement but also a high incidence of complications and in many cases an exacerbation of melasma.[1,2,4–7]

In 2008, Polnikorn reported on a new technique using a subphotothermolysis[3] threshold fluence (average fluence 2–3 J/cm^2) flat beam Q-switched Nd:YAG laser, 5 to 10 passes at 1 to 2 weeks intervals for the treatment of melasma. Subsequent studies by Polnikorn and others from Asia have confirmed the effectiveness of this technique. On average, approximately 70% clearing could be observed after 6 to 10 treatments in one third of the treated cases.[8] Unfortunately, this technique with this device still left a large number of patients with less than optimal results. The use of the Q-Switched Nd:YAG with this technique often referred to as laser toning rapidly gained popularity in North Asian Fitzpatrick skin types II-III. However, in South East and Southern Asia with large populations of Fitzpatrick skin types III, IV, and V, fluences around 2 to 3 J/cm^2 often resulted in mottled hypopigmentation and dyschromia after a series of treatments. These side effects were likely the result of overheating from repeated pulsing at this energy. To address these complications, low fluence (less than 1

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J/cm^2) sessions have been used with some Q-switched laser systems. Unfortunately, this led to poor responses and high rate of recurrence.[9–13]

The introduction of the picosecond Alexandrite laser at 755 nm in 2014 for tattoo removal provided a device with a very high-peak power and a 750 picosecond pulse duration. Theoretically, this picosecond pulsed laser should be able to break and clear epidermal and dermal melanin faster with less thermal injury than the nanosecond pulse. Clinically, we have observed the skin to lighten with low-dose treatments on dark-skinned Asian patients with histological evidence of focal epidermal necrosis and vacuolization (Figure 1).

Shortly, after the delivery of the picosecond Alexandrite laser to our clinics, a set of diffractive lens array became available. These were configured to deliver 0.71 J/cm^2 with the 6 mm optic, 0.41 J/cm^2 with the 8 mm optic, and 0.25 J/cm^2 with the 10 mm optic. These arrays are hexagonal, close packed diffractive lens array which are spaced 500 μm center-to-center. These lens arrays redistribute the light into a multitude of high fluence, tightly focused micro beams embedded in a low fluence background. Approximately, 70% of the total energy is delivered in the high fluence regions which comprise less than 10% of the treatment area. Thirty percent of the energy is delivered in the low fluence background.

The histologies after treatment with these diffractive lenses showed epidermal vacuoles that were found

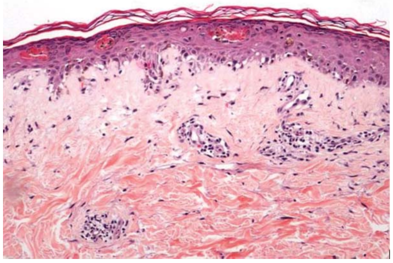

Figure 1. Histology of photo MI 33, ST IV, 24 Hispanic nonsun exposed. Biopsy 24 hours after exposure to 1.6 J/cm^2, flat optic. Prominent liquefaction/necrosis of epidermal keratinocytes with an extensive vacuolar interface reaction. Moderate superficial and mid dermal predominantly lymphocytic inflammation with increased superficial neutrophils. No vasculitis.

in a pattern which corresponded to distribution of the micro lens in the arrays (Figure 2). They seem to be produced by areas of laser-induced optical breakdown (LIOB) from the absorption of high energy 755 nm light by melanin and were confined to the epidermis just below the granular layer without disruption to the basal layer at the dermal–epidermal (DE) junction.[14] These lens arrays with the picosecond Alexandrite laser have been used successfully to treat a variety of skin types including Asian patients and darker skin individuals with skin Types IV, V, and VI for photo damage and acne scars.[15,16] The lightning of the skin was especially noticeable in the darker skin types, which prompted us to consider using this device and lens arrays to treat melasma.

Methods

This human experiment was approved by the Kasemrad Hospital Prachacheun Ethical Committee. The study took place from October 2014 to March 2018. Sixty Thai female patients (Fitzpatrick skin Type IV–VI) with refractory melasma were included in this prospective study. All patients had stopped all previous treatments/medications for at least 1 month before treatment with the picosecond Alexandrite laser. Patients with pregnancy, active dermatitis, or who could not attend follow-up treatments for at least 4 sessions were excluded.

Nineteen patients were treated with the flat optic (1.2–2 J/cm^2) from October 10, 2014 to February 10, 2015. After the diffractive lens array was available, 41 patients were treated from February 2, 2015 to March 13, 2018, with the 8 mm spot 0.41 J/cm^2. Treatments were performed every 2 weeks for 3 months (total of 6 treatments) with follow-up evaluation at 6 months.

Clinical Assessment

Clinical assessment included dermatologic examination of the face and neck by an experienced dermatologist (the author). Skin texture, color, and complications were recorded. For more semi-quantitative evaluation, the Melasma Severity Index (MSI) as had been studied and recommended by Majid

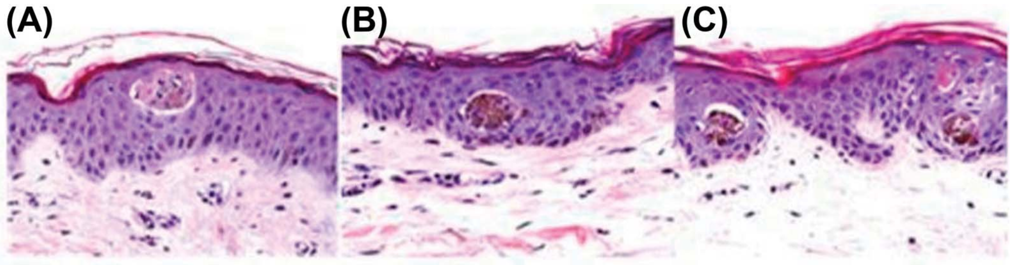

Figure 2. Histology after the diffractive lens array, MI 31 skin Type IV—(A) 6 mm, 0.71 J/cm^2, (B) 8 mm, 0.4 J/cm^2, and (C) 10 mm, 0.25 J/cm^2 optic spot size demonstrating laser- induced optical breakdown (LIOB) with a reduction of melanin density.

and colleagues[17] in 2016 had been applied and replaced Melasma Area Severity Index (MASI) which related more to area than degree of hyperpigmentation and was not correlated well with clinical improvement in the dark skin type (Fitzpatrick skin photo Type IV-V). To enhance accuracy of grading, high-resolution studio-type digital photography (20 MegaPixels, Nikon, Shinagawa, Tokyo Japan) with controlled lighting of front and side views for each patient on every visit were taken. The MSI score was determined by a blinded health care professional using magnified high-resolution digital photography of full left, right, and nose photographs. Melasma Severity Index scores were determined for Day 0 (pretreatment), Day 30, Day 90, and Day 180.

Melasma Severity Index

The MSI was performed using the scoring system that had been purposed for dark skin type by Majid and colleagues in 2016[17] and performed at pretreatment as well as at 3-month and 6-month follow-up sessions. The Melasma Severity Index correlates more with color of the lesions and relates to clinical improvement, whereas the MASI that had been used in the past derived from PASI scores for psoriasis and relates more to the area of the lesions. In dark skin types, the color of lesions is of more cosmetic concern than the area of the lesion. Lighter but wider area of hyperpigmentation with high MASI scores would be regarded as insignificant by most dark skin patients, whereas small area with dark color (low MASI score) is regarded as a more severe lesion. Therefore, in our opinion, MSI scoring is a more accurate assessment of melasma in dark skin types.[17]

The face was divided into 3 areas:

l = left face, r = right face, and n = nose

$$\mathrm{MSI} = 0.4(a \times p^2)l + 0.4(a \times p^2)r + 0.2(a \times p^2)$$

"a" stands for "area of involvement," "p" stands for "severity of pigmentation," "l" for left face, "r" for right face, and "n" for nose.

a = percentage of total area, 0 to 4 (0 = 0, 1 = <10%, 2 = 11% to 30%, 3 = 31% to 60%, and 4 = >60%)

p = pigment intensity, scoring 0 to 4 (0 = none, 1 = barely visible, 2 = mild, 3 = moderate, and 4 = severe)

Treatment Protocol

Group I

Nineteen cases were treated with the picosecond Alexandrite laser flat optic, 1.02 to 1.5 J/cm^2, 3 to 4 mm spot size x1 pass every 2 weeks for 3 months, with follow-up evaluation and MSI score assessment after 3 and 6 months.

Group 2

Forty-one cases were treated with the picosecond Alexandrite laser with diffractive lens array, 0.4 J/cm^2, 8 mm spot size (230 micro beams) with 1 pass. Treatments occurred every 2 weeks for 3 months, with follow-up evaluation and MSI score assessment after 3 and 6 months.

Topical postlaser treatment consisted of topical emollient, sun avoidance, and broad spectrum sun screen, Anthelios XL (SPF 50+. PA ++++, La Roche Posay, France). Prevention and treatment of hyperpigmentation was performed with topical 4% alpha arbutin and 15% ascorbyl phosphate palmitate sodium (F-APPS solution, SAL, Japan).[18]

Statistical Analysis

The mean MSI scores and post-treatment assessment between the groups were performed using SPSS software (version 16.0; SPSS, Inc., Chicago, IL).

Results

For Group I with flat lens treatment (picosecond Alexandrite laser; Hologic-Cynosure Westford, MA), there was immediate grayish discoloration of the lesion. A thin scab would occur and then would fall off after a few days followed by transient hypopigmentation. Pigment would recover within a few weeks. In patients treated with the diffractive lens array, there was only transient erythema usually lasting not more than 1 hour.

Melasma Severity Index

Average baseline MSI scores for Group I were 8.63 which improved to an average score of 3.16 at the 6 months follow-up (Table 1). The MSI score was 2.4 pretreatment, 6.8 after the first month, and 1.2 (50% improvement) at 6 months. There was an average improvement of 57.2% (±36.1%) seen in the flat optic group, which was statistically significant ($p < .001$, 2-tailed paired t-test) (Figure 3). Group II had an average baseline MSI score of 6.22, which improved to an average of 1.48 at the 6 months follow-up. Subjects treated with the diffractive lens array had an average improvement of 75.7% (±47.1%), which was statistically significant ($p < .001$, 2-tailed paired t-test) There was no rebound melasma or hypopigmentation (Figure 4). The difference in improvement between the diffractive lens array and the flat optic was 18.5% ($p = .098$, 2-tailed students unequal variance t-test).

Subject Satisfaction

77.8% of the subjects were satisfied with their results in Group I, whereas subjects in Group II were satisfied 93.0% of the time. Subjects in Group II responded that they were totally satisfied with their results 76.7% of the time, compared with 27.8% of subjects in Group I. 22.2% and 7.0% of subjects in Groups I and II, respectively, were dissatisfied with their results.

Side Effects

In Group I, there were 3 cases (16%) that developed darkening of melasma (recurrence). Four cases (21%) developed macular hypopigmentation lasting more than 6 months. All cases resolved over the next 12 months. This type of complication prompted us to develop a new protocol after the diffractive lens array had been acquired. For Group II with diffractive lens array on the picosecond Alexandrite laser, immediately after treatment, there was mild transient erythema and patients experienced a mild heating sensation that last a few hours. After treatment, there was recurrence of lesions in 2 cases (5%) and no hypopigmentation.

Discussion

The treatment of melasma with lasers and light devices has been both challenging and disappointing. We have had devices which can target melanin in the skin, but using these lasers and light sources have often resulted in rebound hyperpigmentation, presumably from the local thermal effects of these devices on the melanocytes or the surrounding vasculature. Those of us that practice in a sunny climate have experienced even more

TABLE 1. MSI Scores Assessed Throughout the Study

		MSI Scores: Average (SD)			
Group	N =	Baseline	6 Months FU	% Improvement	p-Value
I—Flat optic	19	8.63 (±6.04)	3.16 (±3.23)	57.2% (±36.1%)	<.001
II—Diffractive len array	41	6.22 (±5.75)	1.48 (±3.70)	75.7% (±47.1%)	<.001

MSI, Melasma Severity Index.

Figure 3. Clinical picture of a case in Group 1 before and after 1 and 6 months.

Figure 4. Clinical picture of a case in Group 2, the MSI scores gradually decrease from the pretreatment of 11.2 to 1.1 at 3 months and 0.25 at 6 months.

frustration with our device treatments for this condition because of the solar stimulation that occurs with normal daily activities even with the liberal use of sunscreens and protective clothing. The advent of high-energy picosecond lasers offered another opportunity to re-evaluate the use of short-pulsed devices to treat melasma. We have had modest success using a 755 nm picosecond Alexandrite laser with the flat optic in our patients, but the results have been somewhat inconsistent. In some of our patients who we have biopsied, we have seen evidence of epidermal damage scattered throughout the epidermis but especially noticeable at the DE junction (Figure 1). These histological features all suggest a significant amount of thermal damage which could explain our failures with the flat optic with rebound hyperpigmentation seen in some patients. In patients with lighter skin types living in temperate climates without significant solar stimulation, the use of the flat optic has been used successfully.

The addition of the diffractive lens array to the picosecond Alexandrite laser provided us with an opportunity to explore the delivery of a very high-energy picosecond pulsed laser in a very small area of the epidermis. This resulted in a unique injury in the form of a small 40 to 60 μm vacuole in the granular layer of the epidermis with no visible abnormalities to the surrounding keratinocytes. No damage is routinely observed at the DE junction nor have we observed dermal deposition of the pigment after the treatments.[14] We believe that it is the result of a localized area of LIOB from the absorption of 755 nm light by melanin in the epidermis. These vacuoles or LIOBs seem to form MENDS zones with cellular debris and pigment, which are exfoliated over 2 to 4 weeks. Over a series of treatments with this diffractive optic on this picosecond laser, we have seen improvement in acne scars, photo damage, mottled hyperpigmentation, and lentigines. Some authors have had success with this optic and laser on patients with melasma. We have experienced melasma flares in some of our patients. Our inconsistent results could be in part because of our patient population with many darker skin types and our practices located in sunny areas of the world. It is possible that there is significant thermal stimulation with this treatment when used with 3,000 to 5,000 pulses with 3 to 5 passes to the face. We have demonstrated that although there is very little heat generated during the laser treatment with the diffractive optic, there is a significant temperature rise of 5.6°C that occurs 15 minutes after treatment with 3 to 4 passes with this device on the skin.[19] This heating lasts for a number of hours and could be a factor in the rebound pigmentation that we are seeing in some of our patients with melasma. Therefore, our technique used in this study purposefully uses only 1 pass at 1 Hz with cooling after the treatment to avoid the stimulation and post-treatment heating that occurs with multiple passes.

Arbutin (the topical used post treatment in this study) is a chemical extracted from the leaves of the bearberry, which decreases melanin production by inhibiting tyrosinase activity. The alpha conformation is the more stable form of this chemical making it manageable for skin lightening. This drug has an excellent safety profile and is well tolerated by our patients in Thailand. This product is used in our patients to enhance the outcomes in both groups. By itself, this agent has limited efficacy and is used to maintain a remission.[18]

Although this technique of fractional 755 nm picosecond Alexandrite laser treatment of melasma is better in our hands that the other options, it too can be associated with a worsening of this problem in some patients. In this study, we had cases which worsened or showed minimal improvement in both groups. However, the patients treated with the diffractive lens array had a lower percentage of complications and a better outcome. A comprehensive approach to this problem with selective targeting of melanin appropriated bleaching agents, sun protection, and, in some instances, the use of a systemic agent such as tranexamic acid can all be helpful in addressing this challenging condition.

Conclusions

We have attempted to quantify the effect of the picosecond Alexandrite laser at 755 nm with the diffractive lens array with a slow, low-density technique when it is used to treat a challenging group of Asian melasma patients in a sunny climate.

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