Low-Fluence Q-Switched Neodymium-Doped Yttrium Aluminum Garnet (1,064 nm) Laser for the Treatment of Facial Melasma in Asians

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BACKGROUND Pigment lasers have been used in melasma with unsatisfactory results.

OBJECTIVE To determine the effectiveness and safety of 1,064-nm Q-switched neodymium-doped yttrium aluminum garnet (QS-Nd:YAG) laser treatment of melasma in Asians.

MATERIALS AND METHODS Split-face randomized study comparing combination QS-Nd:YAG laser and 2% hydroquinone with topical treatment in dermal or mixed-type melasma. Twenty-two patients were treated with 1,064-nm QS-Nd:YAG laser, 6-mm spot size, 3.0- to 3.8-J/cm^2 fluence for five sessions at 1-week intervals. Pigmentation was objectively recorded using a colorimeter (lightness index score), and subjective assessments were evaluated using the modified Melasma Area and Severity Index (mMASI) score.

RESULTS After five laser treatments, statistically significant improvement of melasma from baseline was observed in colorimeter ($p<.001$) and mMASI score ($p<.001$) on the laser side. The laser side achieved an average 92.5% improvement in relative lightness index and 75.9% improvement in mMASI, compared with 19.7% and 24%, respectively, on the control side ($p<.001$). Mottled hypopigmentation developed in three patients. During follow-up, four of 22 patients developed rebound hyperpigmentation, and all patients had recurrence of melasma.

CONCLUSION QS-Nd:YAG laser treatment for melasma in Asians produced only temporary improvement and had side effects. Common complications were hypopigmentation, melasma recurrence, and rebound hyperpigmentation.

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Melasma is a common cosmetic problem in Asians. Because of its refractory and recurrent nature, especially the mixed or dermal component, melasma is often difficult to treat.[1] Broad-spectrum (ultraviolet A plus ultraviolet B) sunscreens and topical hydroquinone (HQ) are the most commonly used treatments for melasma. Other topical lightening agents include retinoic acid, azelaic acid, and kojic acid. Physical therapies such as chemical peels, dermabrasion, lasers, and intense pulsed light (IPL) have also been used with varying degrees of success and side effects.[2,3]

There have been some reports of more successful treatment of melasma using resurfacing lasers (erbium:YAG, combination pulsed carbon dioxide (CO_2) laser followed by Q-switched (QS) alexandrite laser (QSAL), and combined ultrapulse CO_2 laser and QSAL) but with significant downtime and frequent postinflammatory hyperpigmentation.[4–6] Recent reports of using fractional resurfacing lasers to treat therapy-resistant melasma have indicated improvement in melasma with less risk and downtime.[7] Melasma has also been treated with various pigment-specific lasers, but the results were disappointing,[8–12] often resulting in severe postinflammatory hyperpigmentation.[13]

In QS-Nd:YAG laser treatment for benign pigmented lesion removal, the laser targets melanin particles

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found within melanocytes, keratinocytes, or dermal melanophages, and multiple treatments are required. Recently Polnikorn described a new technique of repetitive subthreshold pulsed 1,064-nm QS-Nd:YAG laser treatments that was effective for the treatment of refractory dermal melasma.[14]

The objective of the current study was to explore the effectiveness and safety of multiple treatments with a low sub-photothermolytic fluence, 1,064-nm QS-Nd:YAG laser to treat melasma in Asians.

Material and Methods

Study Design

The Ethical Review Committee of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, reviewed and approved the protocol. This was a single-center, split-face, randomized, controlled study comparing a combination of low-fluence QS-Nd:YAG laser and topical 2% hydroquinone cream with topical treatment alone in patients with dermal or mixed-type melasma. Patients were informed of study procedures, risks, benefits, potential complications, and side effects and were included in the study only after signing the informed consent form.

Subjects

Twenty-two healthy Thai patients (21 women and 1 man, mean age 46.8; range 28–60; Fitzpatrick skin type III, $n = 10$; IV, $n = 6$; V, $n = 6$) with clinical diagnosis of dermal and mixed-type melasma were recruited into the trial. Wood's lamp examination was used to determine type of melasma. The average duration of melasma was 8.6 years. Most patients had tried a variety of treatments previously, including topical bleaching agents and chemical peeling or laser (IPL, QS-Nd:YAG, erbium:YAG laser), with little or no improvement.

All subjects had no underlying skin disease or skin lesions on the treatment area, were aged 15 and older, and were not pregnant or breastfeeding. Patients with a history of poor wound healing, abnormal scarring, and photosensitivity and those receiving oral pills, hormone replacement therapy, or topical bleaching agents within 1 month or chemical peeling, laser, or IPL within 6 months of enrollment were excluded.

Laser Treatment

Two weeks before starting laser treatment, all patients were instructed to apply 2% hydroquinone cream (2% Clariderm, Stiefel Laboratories, Bangkok, Thailand) to the lesions on both sides of face once a day at night and to use a broad-spectrum sunscreen with a sun protection factor 60 (Spectraban 60, Stiefel Laboratories) throughout the study. Randomly, one side of the face was treated with a 1,064-nm QS-Nd:YAG laser (MedLite C6, Hoya ConBio, Fremont, CA), 6-mm spot size, collimated homogenous flat-top beam profile, using energy fluences of 3.0 to 3.8 J/cm^2 at 10 Hz for five sessions at 1-week intervals. During the procedure, cooled air ($\sim$20°C) was used to protect the epidermis and to relieve pain. The clinical end point was immediate lightening of pigment or mild erythema without petechiae. The other side of the face received topical treatment alone as a control.

Assessment of Response

Clinical and instrumental evaluations for improvement in pigmentation were conducted at baseline and before and after every treatment session. To assess the persistence of improvement, patients were followed up every 4 weeks for 12 weeks after the last laser treatment. Standard digital photographs (Visia CR, Canfield Imaging Systems, Fairfield, NJ) were taken from the front and side of both cheeks under the same condition at baseline and at each subsequent follow-up visit.

Objective Evaluations

For skin color measurement, a tristimulus colorimeter (Chromometer CR 200, Minolta, Osaka, Japan) was used to objectively quantify changes in skin color using the CIE $L^*a^*b^*$ color system, which

allows a color to be quantified according to three axes: white-black (L^*), red-green (a^*), and yellow-blue (b^*). We used the L^* parameter, which is related to "luminous reflectance" or skin lightness and shows skin reflectance on a gray scale, with values from 0 (black) to 100 (white).[15,16]

An absolute lightness index (L^*I) was defined using five L^* measurements from darkest areas of involvement. A relative L^* index (RL*I), similar to one described by Wang and colleagues,[17] was calculated from the difference of the absolute L^* index between normal skin and melasma.

$$\text{Relative lightness index (RL*I)} = \text{Absolute } L^*\text{I of normal skin} - \text{Absolute } L^*\text{I of melasma}$$

$$\text{Improvement rate}(\%) = \frac{(\text{RL*I pre-treatment} - \text{RL*I post-treatment})}{\text{RL*I pre-treatment}} \times 100$$

An objective assessment of improvement rate was documented as excellent, 76–100%; good, 51–75%; fair, 26–50%; or poor, 0–25% or darker.

Subjective Evaluations

Subjective assessments were evaluated using the modified Melasma Area and Severity Index (mMASI) score to grade the severity of melasma before and after every treatment session. The original Melasma Area and Severity Index (MASI) score[18] evaluated the entire face, but the mMASI score[19] counted only a confined portion of malar (cheek) area and was calculated based on the percentage of involved area (A = 0–6: 0 = 0%, 1 < 10%, 2 = 10–29%, 3 = 30–49%, 4 = 50–69%, 5 = 70–89%, 6 = 90–100%); darkness of pigment (D = 0–4: 0 = absent or normal skin color without evidence of hyperpigmentation, 1 = slight visible hyperpigmentation, 2 = mild visible, 3 = marked, 4 = severe), and homogenicity or density of hyperpigmentation (number of pigmented lesions per unit facial area) (H = 0–4: 0 = minimal, 1 = slight, 2 = mild, 3 = marked, 4 = severe).

$$\text{mMASI} = (\text{darkness of pigment} + \text{homogeneity}) \times \text{area}$$

Two blinded independent dermatologists and the treating dermatologist reviewed the clinical photographs to determine the degree of improvement and scored the mMASI, as well as any complications. In addition, all patients completed a questionnaire to assess their subjective satisfaction with the laser treatment using a 5-point grading system as follows: very satisfied, satisfied, somewhat satisfied, dissatisfied, and very dissatisfied. For the QS-Nd:YAG laser side, the degree of pain was assessed using the visual analogue scale (0–10).

Safety Assessments

Any possible complications and side effects (erythema, edema, burning, petechiae, acute urticaria, postinflammatory hypopigmentation, and hyperpigmentation) were recorded at each visit.

Statistical Analysis

The Wilcoxon rank sum test was used to test baseline equality between the treatment sides and to compare the changes. All tests were assessed at an $\alpha = 0.05$ significance level. $P < 0.05$ defined statistical significance. Values were expressed as means $\pm$ standard deviations.

Results

All 22 subjects completed the study. There were no statistical differences between the two sides in baseline relative lightness index ($p = .45$) or mMASI score ($p = .41$).

Colorimeter Measurement

The difference in skin color between normal skin and melasma skin calculated as the mean relative lightness index (RL*I) measured over time is shown in Figure 1. On the laser side, mean RL*I score decreased significantly, from 4.6 ± 1.9 at baseline to 3.5 ± 1.9 ($p < .001$) after only one session of QS-Nd:YAG laser treatment (at week 3), representing 26.7% improvement in pigmentation, and the trend of the laser side continued to decrease with time to 0.6 ± 1.3 ($p = < .001$) after completing the five

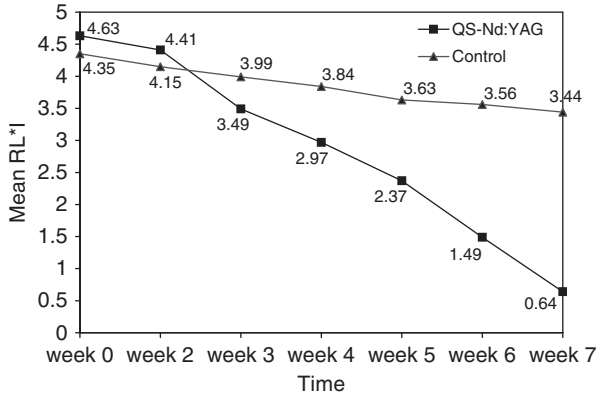

Figure 1. Mean relative lightness index (RL*I) score of Q-switched neodymium-doped yttrium aluminum garnet (QS-Nd:YAG) laser side compared with topical treatment control at different post-treatment intervals. First laser session started after week 2 of topical treatment. Square mark shows QS-Nd:YAG laser-treated side; triangle mark shows topical control side.

treatment sessions, representing a 92.5% improvement from baseline ($p < .001$). The percentage improvement of RL*I from baseline is shown in Figure 2. Excellent improvement (76–100%) was achieved in 16 of 22 treatment sides (72.7%) and good improvement (51–75%) in 4 of 22 (18.2%) (Table 1).

On the control side receiving topical hydroquinone, RL*I show initial improvement after 4 weeks of topical treatment, decreasing from 4.3 ± 1.7 to 3.8 ± 1.8 ($p = .04$), equaling 11.3% improvement and continued to further decrease to 3.4 ± 1.6, representing 19.7% improvement from baseline (Figure 1). Only four of 22 control sides (18.2%) achieved good improvement (51–75%) at the end of treatment, and up to 50% (11/22) of control sides had poor response (0–25% or darker) (Table 1).

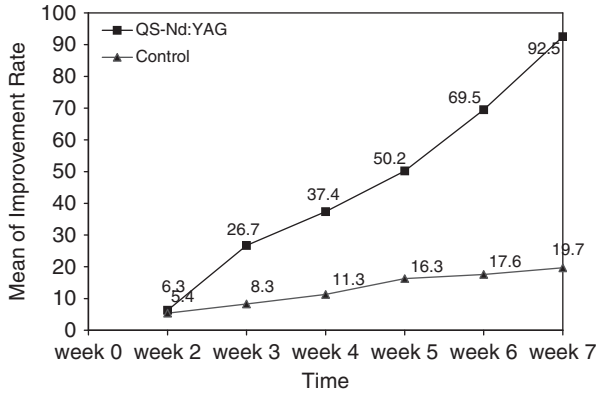

Figure 2. Percentage improvement rate of relative lightness index from baseline over time plot. First laser session started after week 2 of topical treatment. Square mark shows Q-switched neodymium-doped yttrium aluminum garnet laser-treated side; triangle mark shows topical control side.

At week 7, after completing the five laser treatments, both sides had significantly improved responses (reduced relative L^* index score) from baseline, but the difference in mean RL*I between the two sides was clinically and statistically significant in favor of the low-fluence QS-Nd:YAG laser side. This was evident after two laser treatments at week 4 ($p = .005$).

The difference in rate of improvement between the two groups shown in Figure 2 was also found to be significant ($p = .001$), with a better response on the low-fluence QS-Nd:YAG laser side after one session of laser treatment (week 3).

mMASI Assessment

The mean mMASI score of 22 patients over time is shown in Figure 3. On the laser side, mean mMASI score decreased statistically significantly from 22.3 ± 1.8 at baseline to 20.6 ± 1.6 ($p = .001$) after one session of QS-Nd:YAG laser treatment (at week 3), representing a 6.5% reduction in mMASI score. The mMASI score of the laser side continued to decrease with time, to 5.7 ± 0.8 ($p < .001$) after five laser sessions; achieving 75.9% improvement from baseline mMASI ($p < .001$).

On the topical control side, there was initial improvement in mMASI score after 4 weeks of topical treatment, decreasing from 21.9 ± 1.8 to 20.4 ± 1.6 ($p = .003$), a 5.6% reduction.

By 7 weeks, mMASI score on the control side gradually decreased further to 16.6 ± 1.4, or 24% improvement from baseline.

TABLE 1. % Improvement Rate at the End of Laser Treatment Assessed Using Colorimeter

	n *(%)*	
Improvement Rate Assessment	*Low-Fluence Q-Switched Neodymium-Doped Yttrium Aluminum Garnet Laser* (n = *22*)	*Topical Control* (n = *22*)
76–100% (excellent)	16 (72.7)	—
51–75% (good)	4 (18.2)	4 (18.2)
26–50% (fair)	2 (9.1)	7 (31.8)
0–25% or darker (poor)	—	11 (50)

An example of the clinical efficacy of laser treatments is shown in Figure 4A and 4B (before and after pictures of the patient); laser treatment was performed on the left side, and the right side received topical treatment as a control. The difference between the laser-treated and topical control sides is demonstrated in Figure 4C. Figure 5A and 5B shows before and after pictures of the patient; the patient received laser treatment on the left side. We also noticed that most of the patients achieved additional benefits of brighter skin color, smoother skin texture, and uniform pigmentation or a photorejuvenation effect (Figures 4A, 4B, 5A, 5B).

At follow-up, 12 weeks after the last laser session, all of the patients had partial recurrence of melasma, despite the continued use of 2% hydroquinone cream and broad-spectrum sunscreen. Four of 22 patients (18.2%) developed rebound hyperpigmentation on the laser-treated side. Figure 6A and 6B demonstrates the improvement of melasma after laser treatments on the right side, but at 4 weeks of follow-up, the patient developed rebound hyperpigmentation on the laser side (Figure 6C). The other 18 patients had partial recurrence of melasma, with pigmentation less or equal to the control side despite the continuous use of topical 2% hydroquinone. Additional topical bleaching agents and tapering of laser treatments may be necessary to maintain results and prevent rebound hyperpigmentation.

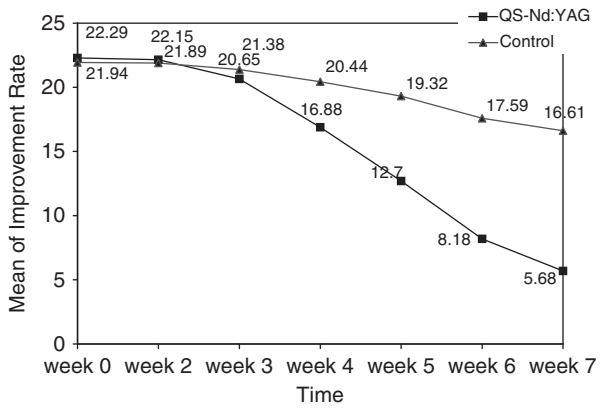

Figure 3. Mean modified Melasma Area and Severity Index score of Q-switched neodymium-doped yttrium aluminum garnet (QS-Nd:YAG) laser side compared with topical treatment control over time plot. First laser session started after week 2 of topical treatment. Square mark shows QS-Nd:YAG laser treated side; triangle mark shows topical control side.

Patient Self-Assessment

Table 2 shows the results of patient's self-evaluation of the degree of improvement of melasma. On the laser-treated side, 19 patients (86.4%) assessed their improvement as very much to much improved (>50% improvement), and the other three (13.6%) assessed their improvement as moderate (50–75%). Compared to the control side, only three patients (13.6%) assessed their improvement as very much to much improved; eight (36.4%) as moderately improved, and 11 (50%) as little or not improved. As for patient satisfaction with the laser treatment, seven (31.8%) were satisfied and 15 were very satisfied with the QS-Nd:YAG laser treatment.

The subjects rated the pain associated with laser treatment at a mean score of 4.7 (range 1–9) on a scale of 1 to 10.

Figure 4. Fifty-five-year-old patient. (A) Baseline, before laser, modified Melasma Area and Severity Index (mMASI) score = 22. (B) After five laser treatments, mMASI score = 6, 72.72% improvement. Improvement in skin texture also noticed. (C) Front view showing the difference between laser-treated side (left) and topical control side (right).

Safety and Side Effects

Few side effects were associated with low-fluence QS-Nd:YAG laser treatment. Erythema, transient burning, and slight edema of the face after treatment were generally mild and disappeared within 1 hour. After completing the five laser treatments, three patients (13.6%) developed mottled hypopigmentation; all were Fitzpatrick skin type V. Figure 7 shows improvement of melasma after laser treatments, but faint hypopigmented spots are also noted, indicating that lower fluences should be used with caution for darker-skinned patients. During the 12-week follow-up period, hypopigmentation in these patients improved, and as mentioned above, melasma recurred in all patients, with rebound hyperpigmentation in four patients.

After completing the whole study period of five weekly laser treatments and follow-up, almost all

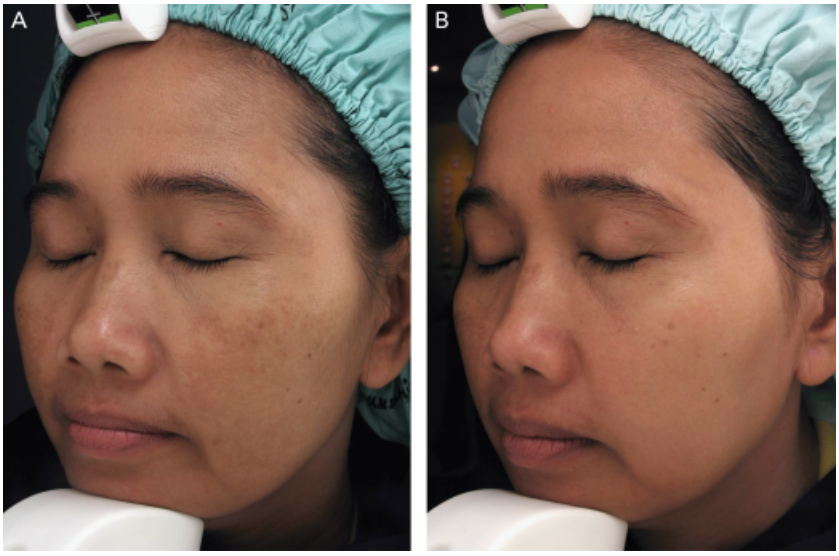

Figure 5. Forty-three-year-old patient. (A) Left side, before laser treatment, modified Melasma Area and Severity Index (mMASI) score = 28. (B) Left side, after five laser treatments, mMASI = 1.67, 94% improvement; also with improvement of skin texture.

patients underwent another five to 10 additional weekly QS-Nd:YAG laser treatments to both sides of the face to treat their recurrent melasma. We encountered approximately eight of 22 cases developing "confetti-like" hypopigmented macules, some with surrounding melasma and hyperpigmentation that was disfiguring in darker skin types. We observed that this complication occurred after receiving multiple (almost 10) laser treatments. Figure 8 shows one patient after receiving 11 weekly QS-Nd:YAG laser treatments.

Discussion

The effectiveness of lasers in pigmented lesions is based on the theory of selective photothermolysis introduced by Anderson and Parrish, which states that, when a specific wavelength of energy is delivered in a period of time shorter than the thermal relaxation time of the target chromophore, heat and injury are restricted to the target, with less damage to the surrounding tissue.[20] The thermal relaxation time of melanosomes ranges from 50 to 500 nsec, and the absorption spectrum of melanin is broad. IPL and short-pulsed pigment-specific lasers using standard fluences, some combined with ablative lasers, have been used in melasma, with varying results, often with side effects, especially postinflammatory hyperpigmentation.[8–13,17,21,22]

The pathophysiology of melasma is unknown. An abnormal epidermis, abnormal dermis, or overactive melanocytes may cause melasma. There is a greater number and more activity of melanocytes, resulting in a large amount of melanosome transfer to the epidermis and dermis. The clinical and histologic characteristics of melasma vary according to the location of melanin. Three patterns of melasma pigmentation are recognized: an epidermal type with hyperactive epidermal melanocytes and pigment deposit in the basal or suprabasal layer; a dermal type with melanin-laden macrophages in the superficial and mid-dermis, especially around the perivascular melanophages; and the mixed type, featuring the epidermal and dermal type with hyperactive epidermal melanocytes and dermal melanophages.[23,24] The histopathology of the melanin pigment in dermal and mixed melasma is similar to tattoo pigment. It has been shown that a single laser session for tattoo

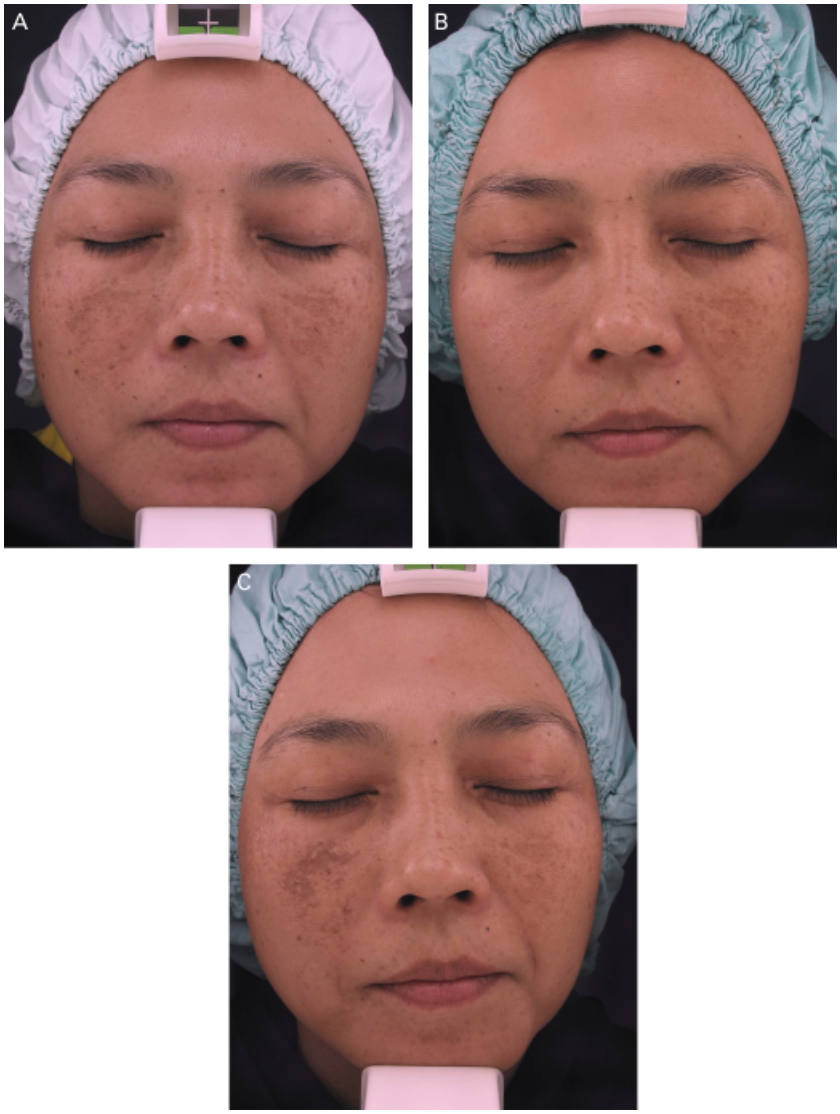

Figure 6. Forty-one-year-old patient. (A) Baseline before, right side modified Melasma Area and Severity Index (mMASI) score = 21, left side mMASI score = 22. (B) After laser treatments, right side mMASI score = 4, compared to topical control left side mMASI score = 14.33. (C) At follow-up 1 month after last laser session, rebound hyperpigmentation is seen only on the laser-treated side.

removal with pigment laser is slow and that multiple treatments are required.

In the past, the use of pigmented lesion dye laser (510 nm), frequency-doubled QS-Nd:YAG (532 nm), QS-ruby laser (694 nm), and QSAL (755 nm) have been used to treat melasma, with disappointing results, some with worse postinflammatory hyperpigmentation. The near-infrared 1,064-nm QS-Nd:YAG has a longer wavelength (> 600 nm), which is well absorbed by melanin and to a lesser extent by hemoglobin, making it generally safer in darker skin types because it spares injury to the epidermis to a greater degree than shorter wavelengths. It has the added benefit of deeper skin penetration. However, in Asian skin, postinflammatory hyperpigmentation is common after 1,064-nm QS-Nd:YAG laser treatments.[25]

TABLE 2. Patient Self-Assessment of Degree of Melasma Improvement

	n *(%)*	
Improvement of Melasma	*Low-Fluence Q-Switched Neodymium-Doped Yttrium Aluminum Garnet Laser* (n = *22*)	*Topical Control* (n = *22*)
Very much improved (76–100%)	10 (45.5)	—
Much improved (51–75%)	9 (40.9)	3 (13.6)
Moderately improved (26–50%)	3 (13.6)	8 (36.4)
Little improved (1–25%)	—	7 (31.8)
Not improved or worse	—	4 (18.2)

Polnikorn reported two case treatments of refractory dermal melasma using 10 weekly treatments with the 1,064-nm QS-Nd:YAG laser at sub-threshold photothermolytic fluences ($< 5\ J/cm^2$), resulting in reduction of epidermal and dermal pigmentation with no recurrences at 1-year and 6-month follow-up respectively.[14] Our data show that five weekly treatments of low-fluence 1,064-nm QS-Nd:YAG laser is an effective treatment for dermal and mixed melasma. In this study, we used a colorimeter to allow more accurate and objective quantification of pigmentation and the split-face study design to eliminate the problem of individual variability. We also showed that colorimeter measurements correlated with subjective clinical evaluation using the mMASI score. We demonstrated that this treatment without downtime produced significant and rapid results, although after five laser sessions, the results were not curative, and recurrence of melasma was the rule. Adding other therapeutic options[2,3] to the topical 2% hydroquinone used in our study may have more successfully maintained the treatment results.

We emphasize that this treatment, although it produced initial beneficial results to patients, was not without side effects. After the five laser treatments, 13.6% (3/22 patients) developed faint, spotty hypopigmentation that improved during follow-up. All cases had recurrence of melasma within the 12-week follow-up; with 18.2% (4/22 patients) experiencing

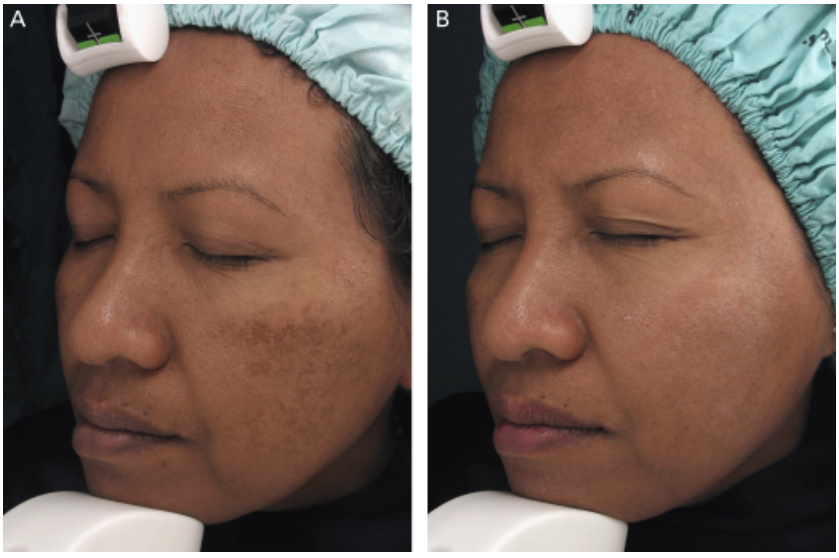

Figure 7. Forty-four-year old patient. (A) Before laser modified Melasma Area and Severity Index (mMASI) score = 23.67. (B) After five laser treatments, decrease in mMASI score to 11.67 and clinical improvement in melasma with ill-defined mottling hypopigmentation on left cheek.

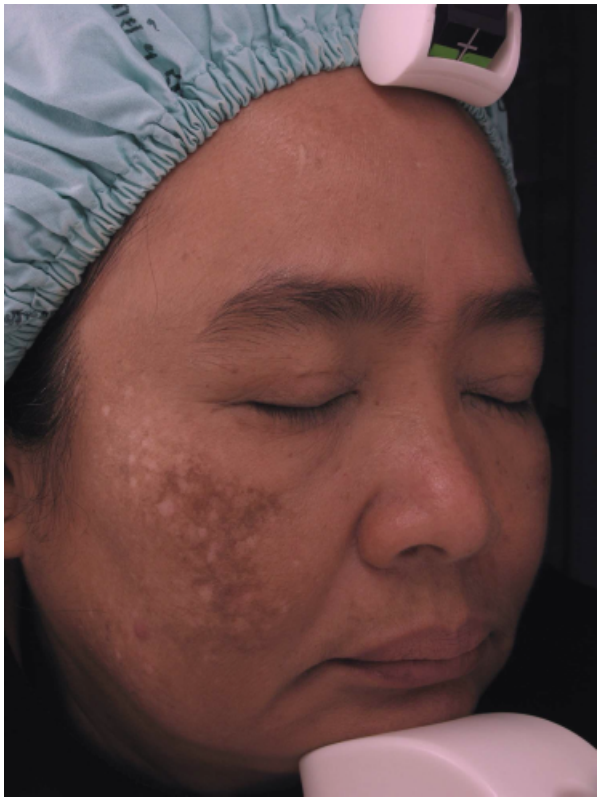

Figure 8. Multiple hypopigmented–depigmented macules interspersed with mottled hyperpigmented macules in one patient after receiving 11 weekly Q-switched neodymium-doped yttrium aluminum garnet laser treatments for melasma.

rebound hyperpigmentation. Therefore, after completing the study period, many patients sought additional once-weekly laser treatments to treat their recurrent melasma, and many patients came back with side effects of disfiguring hypopigmented macules intermingled with mottling hyperpigmented macules in areas of melasma. Tan and colleagues reported two cases of biopsy-proven hydroquinone-induced exogenous ochronosis. One of these two cases had also undergone 1,064-nm QS-Nd:YAG laser therapy for worsening melasma, and the clinical examination described mottled, reticulate, lace-like hyperpigmented macules of ochronosis with confetti-like hypopigmented macules similar to our patients.[26] Mottled hypopigmentation has also been reported after QS-Nd:YAG laser for skin rejuvenation.[27]

After treatment of benign acquired melanocytic nevi with QS lasers, reduction of epidermal melanocytes and numbers of functional and dermal melanocytic nests was noted, with increased dermal melanophages and mild dermal fibrosis.[28]The QS-Nd:YAG (1,064 nm) laser has been shown to cause dermal and epidermal melanosome rupture, melanosome rupture in melanocytes, and destruction of dermal melanophages.[29,30] Anderson and colleagues[30] conducted a study examining selective photothermolysis of cutaneous pigmentation using QS-Nd:YAG laser after single-pulse exposures at 1,064, 532, and 355 nm in guinea pigs, demonstrating melanosome rupture within melanocytes and keratinocytes. Only 532 and 1,064 nm at threshold and suprathreshold exposures produced permanent leukotrichia due to follicular depigmentation. At sub-threshold exposures, none of the three wavelengths caused hypopigmentation, but they stimulated melanogenesis and prominence of dendritic melanocytes in guinea pig skin. From our results, we postulate that the initial lightening of melasma was due to melanin granule dispersion and fragmentation. The laser treatment may also produce nonspecific dermal wound and induce inflammation, which facilitates migration of melanophages. There was no epidermal disruption when low fluence was used, but the inflammation may cause increased epidermal turnover. Repeated laser treatments may reduce or exhaust hyperactive melanocytes, which may be the cause of confetti-like hypopigmented macules. We observed that the complication of mottled hypopigmentation after melasma treatment occurs gradually and often significantly affects the patient. Treatment of hypopigmentation is difficult and may lead to worsening of the melasma; at the same time, bleaching agents can cause worsening of hypopigmentation. Alternatively, multiple subthreshold exposures to the 1,064-nm wavelength may stimulate melanogenesis in some areas and produce rebound hyperpigmentation similar to the guinea pig model.[30] Therefore, to avoid these serious complications, we caution the use of too many (more than 5 approaching up to 10 treatments) or too frequent (every week) QS-Nd:YAG laser sessions. We propose that the

observation of even slight hypopigmentation should contraindicate further treatment with sub-threshold fluence, 1,064-nm QS-Nd:YAG lasers.

Most of the patients also observed the benefits of improvement in skin texture and lightened skin color on the laser-treated side. Textural changes such as this are thought to be the result of collagen remodeling and are the basis of improvement seen with treatment of photoaged skin or "photorejuvenation effect" using nonablative lasers. The nonablative, dermal remodeling effects of the 1,064-nm QS-Nd:YAG laser in the treatment of wrinkles and atrophic acne scars have been clinically and histologically confirmed.[31–37]

The repeated use of nonablative lasers and light sources for skin rejuvenation and melasma can be addictive to patients because there is no downtime. Therefore, the effect of repeated exposure to longer wavelength radiation in human skin is an important issue to be considered. An in vitro study by Chan and colleagues[38] on the effect of sublethal QS 755-nm lasers on the expression of p16INK4a in melanoma cell lines found that sublethal laser damage could increase DNA damage, which leads to greater p16 expression. More recently, Chan and colleagues further demonstrated in an animal study that repeated treatment with high-energy laser and IPL exposure, although it did not cause any toxicity or tumor in mice, produced elevations of p16 and proliferating cell nuclear antigen expression, indicating DNA damage.[27] The long-term safety of large-spot-size, low-fluence QS-Nd:YAG laser in the treatment of melasma and skin rejuvenation is not known and should be further studied.

Multiple treatments with a 1,064-nm QS-Nd:YAG laser at lower sub-photothermolytic fluence for treatment of dermal and mixed melasma produced only temporary improvement of melasma (MASI, chromometer pigmentation measurements). However, complications of recurrent melasma, rebound hyperpigmentation, and mottled hypopigmentation were common, making this a discouraging treatment for melasma. We caution the use of this laser treatment to more than five once-weekly treatments with the careful surveillance of development of hypopigmentation or leucoderma, which should contraindicate further QS-Nd:YAG laser treatments. The long-term safety of this treatment protocol needs to be studied because the total cumulative energy after multiple subthreshold laser treatments may be higher than used in standard energy treatment.

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