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ORIGINAL ARTICLE

Treatment of melasma by low-fluence 1064 nm Q-switched Nd:YAG laser

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Background: **Low-fluence 1064 nm Q-switched Nd:YAG laser has recently been shown to be effective for the melasma treatment.** ***Objective*****: The purpose of this study is to evaluate the clinical efficacy and safety of low-fluence 1064 nm Q-switched Nd:YAG laser treatment of melasma in Asian patients.** ***Methods:*** **Fifty patients with melasma underwent 15 weeks of weekly treatments, using a Q-switched Nd:YAG laser (RevLite®; HOYA ConBio®, Freemont, CA, USA) at 1064 nm with an 8-mm spot size, and a fluence of 2.8 J/cm^2. Patients and investigators subjectively evaluated the intensity of pigmentation after completion of 15 weekly treatments. The objective assessment was also performed with digital photographs and a pigment imaging tool (Janus®, PSI Co., Ltd., KOREA).** ***Results*****: Both patients and investigators rated the treatment outcome as "good improvement" on average with improvement rate of 50–74%. The pigment imaging technology system also confirmed the improvement of the pigmentation level on all three locations of the face. None of the 50 patients showed any signs of severe side effects during the course of the treatment.** ***Conclusion:*** **Low-fluence 1064 nm Q-switched Nd:YAG laser is an effective method to treat melasma without serious side effects in Asian patients.**

Key words: low-fluence 1064 nm Q-switched Nd:YAG laser, melasma

Introduction

Melasma is a common pigmentation lesion of the skin and it predominantly affects women with darker complexions. Among various etiologic factors including genetic predisposition and hormonal influences, exposure to UV light plays key role in pathogenesis of melasma. Melasma is often refractory to chemical peels, topical therapy with hydroquinone, retinoids, azelaic or kojic acids due to resistance to the agent and rapid recurrence of the lesion (1–5).

Laser therapy is gaining popularity. Several laser systems such as carbon dioxide or Q-switched alexandrite (755 nm) are reported to improve hyperpigmentation. However, high rates of post-inflammatory hyperpigmentation and/or long downtime rates were commonly observed, as well as melasma recurrence (6,7). Q-switched frequency doubled the neodymium:yttrium–aluminum–garnet (Nd:YAG, 1064/532 nm) and the Q-switched ruby (694 nm) lasers failed in treating melasma, using the high-fluence modus (8,9). Recently, low-fluence Q-switched Nd:YAG lasers proved to be reliable in the treatment of melasma of the skin types III and IV (10,11). However, sample size of the previous studies was small. All the previous studies on melasma treatment had sample size of less than 50 patients.

Accordingly, the authors treated 50 Asian female patients with melasma using a low-fluence 1064 nm Q-switched Nd:YAG laser and evaluated the degree of the improvement.

Materials and methods

The study protocol and consent form were approved by the Institutional Review Board of Soonchunhyang Hospital, Korea. Risks, benefits, and potential complications were explained to all the participants and written informed consents were obtained prior to any treatment.

A total of 50 female patients aged 36–52 years with melasma were enrolled in the study. The patients underwent 15 weekly full-facial treatments using a Q-switched Nd:YAG laser at 1064 nm, which is thought to produce both photothermal and photoacoustic effects in the tissue (RevLite, HOYA ConBio, Freemont, CA, USA). No anesthesia was necessary prior to the treatment (an 8-mm spot size, fluence of 2.8 J/cm^2, 10 Hz). When mild erythema appeared without petechia around the melasma lesion, laser therapy was discontinued.

No patients used hydroquinone or any other topical agents containing α-hydroxy acid and retinoic acid during the treatments. They did not receive any other laser therapies or chemical peels on their faces at least 3 months before and during the treatment. Patients were advised to avoid sun exposure and apply broad-spectrum sunscreen during and after the treatment.

High-quality digital photographs of the patients were taken before initiating treatment and after completion of 15 sessions. Post-treatment improvements were graded by subjects with a questionnaire after completion of 15 weekly sessions. Three investigators also graded treatment outcomes by comparing before and after photos of the patients on a quartile scale (0 = no improvement, "none"; 1 = 1–24% improvement, "poor"; 2 = 25–49% improvement, "fair"; 3 = 50–74% improvement, "good"; 4 = 75–100% improvement, "excellent"). Objective measurement of pigment distribution was obtained with a pigment imaging technology system (Janus®, PSI Co., Ltd., Korea). Janus system analyzes facial skin using three different types of light exposure: normal, polarized, and ultraviolet light. Intensity of pigmentation at right and left cheeks, nose, periorbital area, eye rims, and forehead were calculated. Photographs of patients' faces were taken at three different angles (frontal, left lateral, and right lateral), and the average intensity of pigmentation at each angle was measured on a 100-point scale. Improvement of discoloration

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Table I. Subjective evaluation by patients.

Improvement	Score	Number of patients
None (0% improvement)	0	0
Poor (1–24% improvement)	1	5
Fair (25–49% improvement)	2	7
Good (50–74% improvement)	3	20
Excellent (75–100% improvement)	4	18

was analyzed by reviewing the photographs before initiating the treatment and after completion of 15 weekly treatments.

At each visit, side effects of low-fluence Q-switched Nd:YAG laser therapy were assessed. Patients were examined for presence of side effects such as persistent erythema, postinflammatory hyperpigmentation, or postinflammatory hypopigmentation during and after the treatment.

Measured values were expressed as the means ± standard deviations. Paired t-test and Wilcoxon signed-rank test were performed with SPSS statistical software (SPSS 18.0 Inc., Chicago, IL, USA) to compare the treatment response between the two groups. A p-value of < 0.05 was considered significant.

Results

Demographic data

A total of 50 patients (age 40.14 ± 4.35) were enrolled. All patients were suffering from severe melasma for average of 4.47 years (SD 2.49, range 1.5–12). Patients had history of previous treatment before and all the previous treatment were stopped at least 6 months prior to the study.

Treatment effectiveness

Subjective evaluation by the patient.

Clinical improvements were subjectively assessed by the patients after completing 15 sessions of the treatment. The results of the subjective evaluations were as follows: "none" – 0 persons; "poor" – 5 persons; "fair" – 7 persons; "good" – 20 persons; and "excellent" – 18 persons (Table I). The average score was 3.02, which corresponded to 50–74% improvement ("good").

Evaluation by investigators.

The level of improvement was also subjectively evaluated by three investigators by comparing before and after photographs of the patients (Figure 1). The results were as follows: "none" – 0 persons; "poor" – 4 persons; "fair" – 8 persons; "good" – 17 persons; and "excellent" – 21 persons (Table II). The average score was 3.10, which corresponded to 50–74% improvement ("good").

The average scores of the improvement level measured by patients and investigators were 3.02 and 3.10, respectively. No statistically significant difference was found between the average scores of the two groups (Figure 2).

Objective evaluation of pigment distribution by Janus imaging system.

Clinical improvements in patients were also measured by Janus imaging system (Figures 3–5). Average of the pigmentation level for the 50 patients was calculated (Figure 6). Prior to the treatment, average pigmentation levels were 19.66, 18.70, and 17.60 on the front, left, and right side, respectively. After the completion of the treatment, average pigmentation levels were 15.62, 14.12, and 13.32 on the front, left, and right side, respectively. Differences of the measurement between before, and after

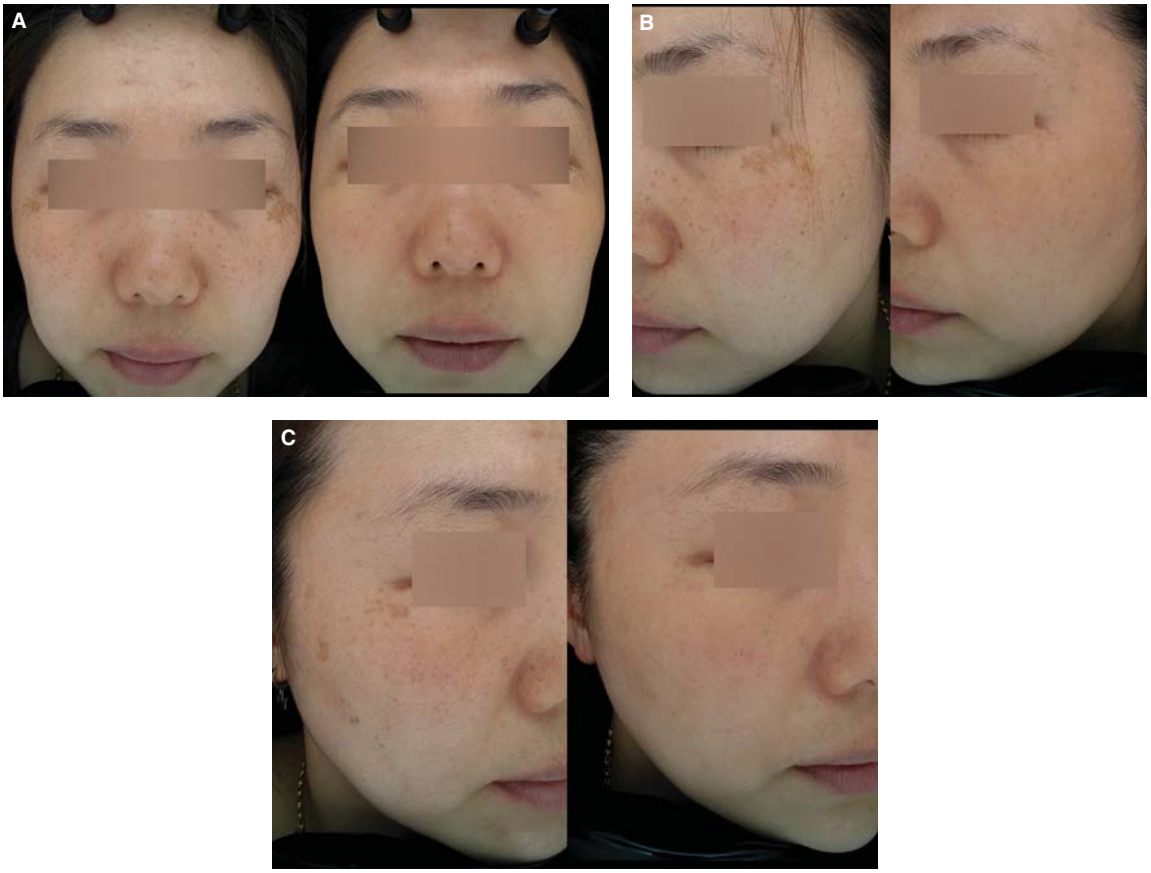


Figure 1. A–C 45-year-old patient (A – front; B – left side; C – right side). Left: Before laser treatment; right: after laser treatment (photographed in general light). After 15 weekly treatments, both patients and investigators graded the treatment outcome as "excellent improvement".

Table II. Subjective evaluation by investigators.

Improvement	Score	Number of patients
None (0% improvement)	0	0
Poor (1–24% improvement)	1	4
Fair (25–49% improvement)	2	8
Good (50–74% improvement)	3	17
Excellent (75–100% improvement)	4	21

treatment were 4.04, 4.58, and 4.28 on the front, left, and right side, respectively. A significant difference in pigmentation levels was found between before and after the treatment on the front, right, and left side (Figure 7).

Safety and side effects

Few side effects were associated with the low-fluence Q-switched Nd:YAG laser treatment. Although most patients experienced erythema, transient burning and slight edema, it was generally mild, and such conditions subsided within 1 to 24 h. There were also no significant serious adverse reactions such as postinflammatory hyperpigmentation or hypopigmentation from the procedure. All 50 patients completed 15-week treatments without any serious complications.

Discussion

Over the last few years, 1064 nm Q-switched Nd:YAG laser has increasingly been referred to as ''laser toning'' for non-ablative skin rejuvenation and melasma in Asian countries. In laser toning, multiple passes of low-fluence laser (e.g., 1.6–3.5 J/cm^2) are delivered through a large spot size (e.g., 6–8 mm) to optimize the energy delivery and to achieve mild erythema, as the clinical end point. The intention is to have multiple laser treatments at subthreshold fluences to potentially obtain clinical improvement with lower down time. Due to minimal down time, some clinicians have proposed daily use of laser toning for skin rejuvenation, while others prefer weekly, bi-weekly, or monthly intervals.

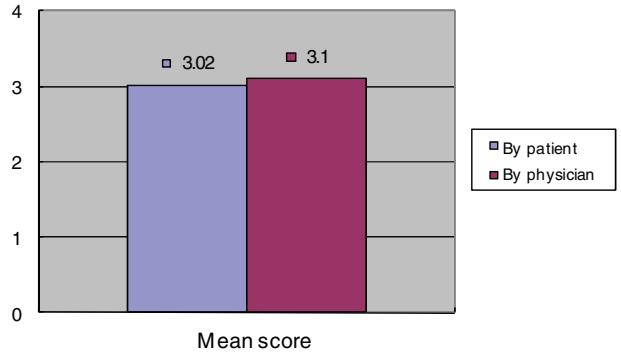


Figure 2. Evaluation of improvement by patients and investigators – Comparison of mean score. Scores: 0 – "none" (0% improvement); 1 – "poor" (1–24% improvement); 2 – "fair" (25–49% improvement); 3 – "good" (50–74% improvement); 4 – "excellent" (75–100% improvement).

Several investigators reported successful treatment of melasma with the laser toning. Polnikorn (12) presented two cases of

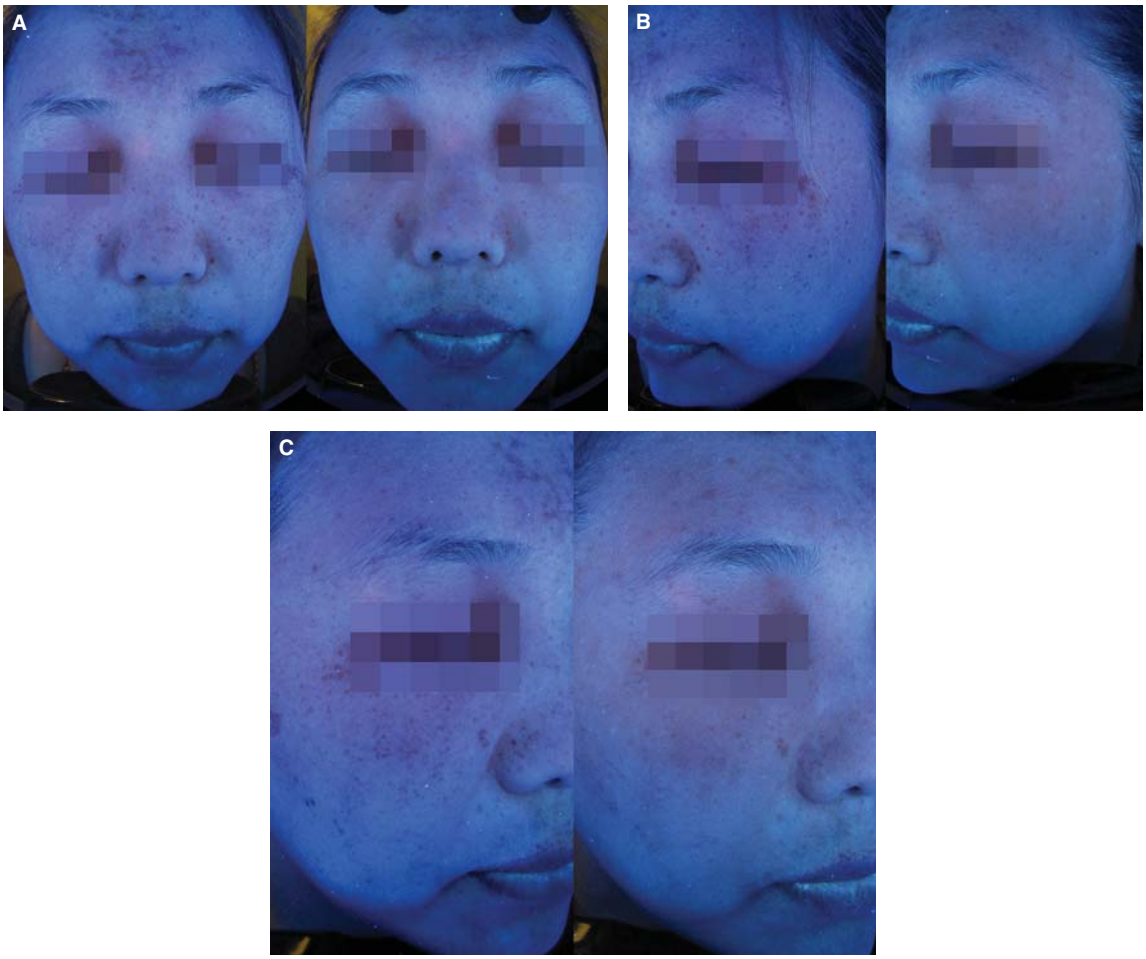


Figure 3. A–C 45-year-old patient (A – front; B – left side; C: – right side). Left: before the treatment; right: after the treatment (photographed in ultraviolet rays). After 15 weekly treatments, patients and investigators rated the treatment outcome as "excellent improvement".

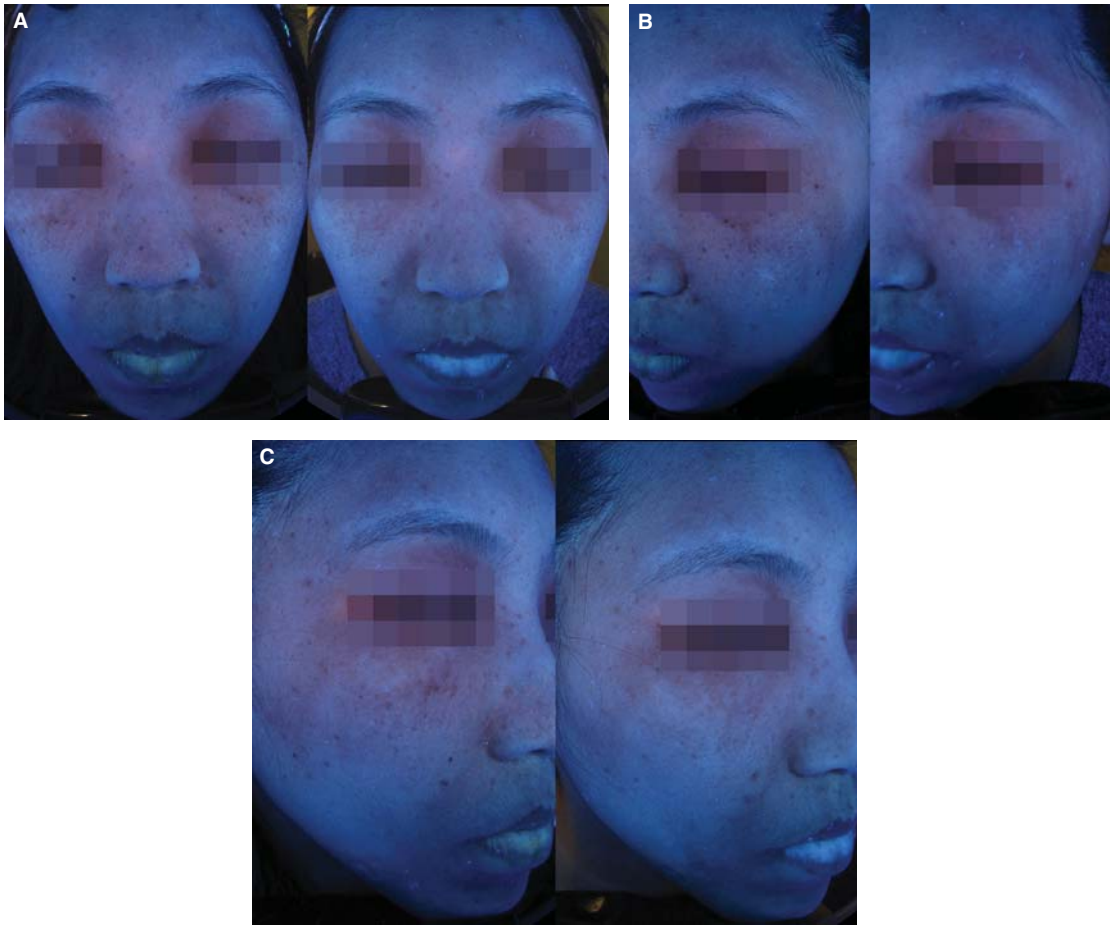


Figure 4. A–C 37-year-old patient (A – front; B – left side; C: – right side). Left: before the treatment; right: after the treatment (photographed in ultraviolet rays). After 15 weekly treatments, both patients and investigators rated the treatment outcome as "excellent improvement".

refractory dermal melasma in which melasma lesions were successfully resolved with a combination of 1064 nm Q-switched Nd:YAG laser (Medlite C6, HOYA ConBio) and a topical 7% alpha arbutin solution. Two female Asian patients received 10 weekly laser treatments (3.4 J/cm^2, 10 Hz, 6 mm spot size, 20 passes in total). Greater than 80% reduction of the epidermal and dermal hyperpigmentation was achieved with no recurrence at 6-month and 1-year follow up. However, it should be noted that the author used a topical 7% alpha arbutin solution in addition to the laser therapy. More recently, Wattanakrai et al. (13) treated 22 patients with melasma in a split-face trial. They compared combined treatment of sub-thermolytic Q-switched Nd:YAG and 2% hydroquinone with 2% hydroquinone alone. After five weekly treatments, improvement in the relative lightness index was significantly higher in the experiment side (Q-switched Nd:YAG with 2% hydroquinone) than in the control side. Using the same device, Cho et al. treated 25 women with melasma (2.5–5 J/cm^2, 6–8 mm spot sizes) and achieved marked clinical improvements in 44% of the patients treated after multiple sessions of treatment (14). In our study, 50 Asian women were treated once a week for 15 weeks with a 1064 nm Q-switched Nd:YAG laser (fluence of 2.8 J/cm^2, 8-mm spot size, 10 Hz). Both patients and investigators noted similar (50–74%) improvement. Pigmentation level of the patients was numerically measured with the pigment imaging system on the front, left, and right sides of the face. The degree of improvement was evaluated. Statistically significant difference of the pigmentation level was found between before and after the treatments. Efficacy of the laser treatment was confirmed by UV photographs of the patients, which analyzed the pigment level using a numeric scale.

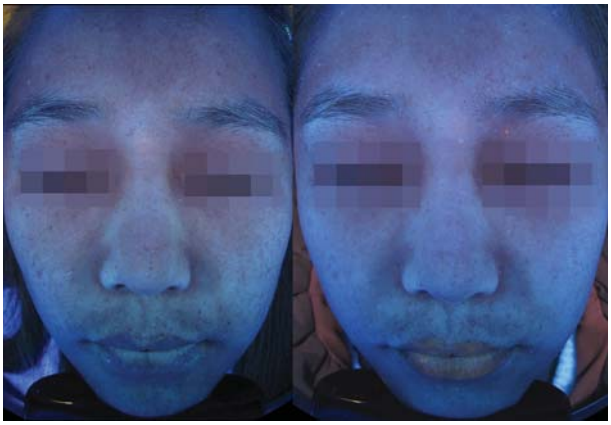


Figure 5. Forty-two–year-old patient (front). Left: before the treatment, right: after the treatment (photographed in ultraviolet rays). After 15 sessions of laser treatment, both patients and investigators rated the treatment outcome as "excellent improvement".

The exact mechanism of laser toning on the improvement of melasma is still unclear. It has been proposed that melanin granules are fragmented and dispersed into the cytoplasm without cellular destruction by repetitive laser energy with a sub-photothermolytic fluence (<5 J/cm^2) over large spot size. "Subcellular selective photothermolysis (SSP)" describes how laser toning improves melasma lesions. Mun et al. (15)

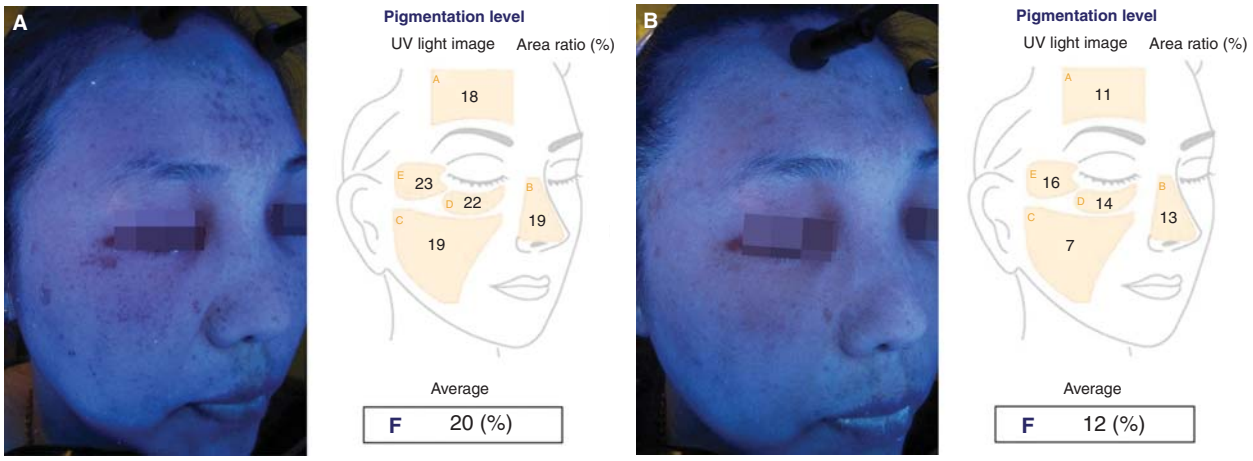
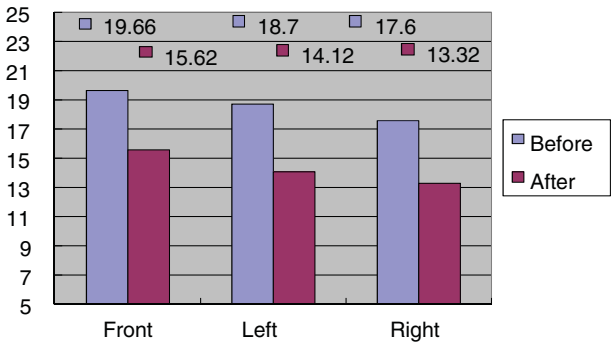


Figure 6. Diagram that measures and shows pigmentation intensity by comparing between before (A) and after (B) treatment with Janus imaging system (Box on the bottom shows the average amount of pigmentation before and after treatment).

investigated ultrastructural changes in melanocytes and melanosomes after low-fluence Q-switched Nd:YAG laser treatment (7 mm spot size, 1.6–2.0 J/cm^2, two passes) in patients with melasma. The volume of the melanocytes, the number of melanosomes, and connecting melanocytic dendrites were considerably reduced in epidermis after the laser treatment. Because mature melanosomes accumulate in the dendrites of melanocytes, selective photothermolytic effect of the laser can be focused intensively on the dendrites. Therefore, this result can also be interpreted as selective photothermolytic effect of the laser on mature melanosomes. Low-fluence Q-switched Nd:YAG laser treatment achieved selective photothermolytic effect on subcellular-specific organelle melanin.

Previous literatures have not fully investigated side effects of laser toning for skin rejuvenation and melasma treatment. Treatment outcomes of melasma are inconsistent and unpredictable with laser and light therapy (16–20). Melasma lesions can recur or get darkened and rebound hyperpigmentation can occur. Laser toning can also potentially unmask previously subclinical melasma. These complications are probably due to sublethal damage or stimulation of hyperactive melanocytes, which may further increase melanin production and results in hyperpigmentation (21). Other complications of laser toning include physical urticaria, acneiform eruption, minute petechiae, whitening of fine facial hair, herpes simplex reactivation, leukoderma, and mottled hypopigmentation (12). This study also closely monitored all patients for above-mentioned side effects and observed no signs of severe side effects such as postinflammatory hyperpigmenation or mottled hypopigmentation.

Non-ablative therapies with lasers and other light sources for skin rejuvenation and melasma treatment can be a habit forming due to minimal downtime. Therefore, effects of repeated exposure to longer wavelength radiation in human skin are important issues to consider. An *in vitro* study by Chan et al. (22) on the effects of sublethal Q-switched 755 nm lasers on the expression of p16INK4a in melanoma cell lines found that the sublethal laser was able to potentially increase DNA damage leading to greater p16 expression. More recently, Chan et al. (23) further



	Before treatment	After treatment	*p* - values
Front	19.66 ± 5.28	15.62 ± 4.31	<0.01
Left	18.70 ± 4.54	14.12 ± 3.85	<0.01
Right	17.60 ± 4.25	13.32 ± 3.38	<0.01

Figure 7. Objective evaluation of pigment distribution by Janus imaging system.

demonstrated in an animal study that repeated exposure to high-energy laser and IPL resulted in elevations of p16 and proliferating cell nuclear antigen expression, indicating DNA damage, although it did not cause any toxicity or tumor in mice. Long-term safety of large spot size, low-fluence Q-switched Nd:YAG laser for the treatment of melasma and further studies are required.

Melasma lesions were improved by multiple sessions of 1064 nm Q-switched Nd:YAG laser therapy at lower sub-thermolytic fluence. Treatment outcomes were subjectively evaluated by both patients and investigators and objectively assessed by the pigment imaging system.

Unlike previous studies, this study investigated low-fluence Q-switched Nd:YAG laser treatment on 50 patients. To our knowledge, no prior studies included such a large sample size. This study was meaningful because melasma was improved after 15 weekly treatments without any side effects in all of 50 participants. Clinical improvement was both subjectively and objectively verified. Because treating melasma with low-fluence 1064 nm Q-switched Nd:YAG laser is relatively simple and noninvasive, it does not affect patients' daily life activities. Therefore, low-fluence 1064 nm Q-switched Nd:YAG laser will become the main treatment modality for melasma in Asians in the near future.

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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. Khunger N, Sarkar R, Jain RK. Tretinoin peels versus glycolic acid peels in the treatment of melasma in dark-skinned patients. Dermatol Surg. 2004;30:756–760.
2. Sarkar R, Kaur C, Bhalla M, Kanwar AJ. The combination of glycolic acid peels with a topical regimen in the treatment of melasma in darkskinned patients: a comparative study. Dermatol Surg. 2002;28: 828–832.
3. Gupta AK, Gover MD, Nouri K, Taylor S. The treatment of melasma: a review of clinical trials. J Am Acad Dermatol. 2006;55:1048–1065.
4. Hurley ME, Guevara IL, Gonzales RM, Pandya AG. Efficacy of glycolic acid peels in the treatment of melasma. Arch Dermatol. 2002;138: 1578–1582.
5. Cestari T, Arellano I, Hexsel D, Ortonne JP. Melasma in Latin America: options for therapy and treatment algorithm. J Eur Acad Dermatol Venereol. 2009;23:760–772.
6. Manaloto RM, Alster T. Erbium:YAG laser resurfacing for refractory melasma. Dermatol Surg. 1999;25:121–123.
7. Nouri K, Bowes L, Chartier T, Romagosa R, Spencer J. Combination treatment of melasma with pulsed CO2 laser followed by Q-switched alexandrite laser: a pilot study. Dermatol Surg. 1999;25:494–497.
8. Tse Y, Levine VJ, McClain SA, Ashinoff R. The removal of cutaneous pigmented lesions with the Q-switched ruby laser and the Q-switched neodymium: yttrium-aluminum-garnet laser. A comparative study. J Dermatol Surg Oncol. 1994;20:795–800.
9. Goldberg DJ. Benign pigmented lesions of the skin. Treatment with the Q-switched ruby laser. J Dermatol Surg Oncol. 1993;19:376–379.
10. Jeong SY, Shin JB, Yeo UC, Kim WS, Kim IH. Low-fluence Q-switched neodymium-doped yttrium aluminum garnet laser for melasma with pre- or post-treatment triple combination cream. Dermatol Surg. 2010; 36:909–918.
11. Choi M, Choi JW, Lee SY, Choi SY, Park HJ, Park KC, et al. Low-dose 1064-nm Q-switched Nd:YAG laser for the treatment of melasma. J Dermatolog Treat. 2010;21:224–228.
12. Polnikorn N. Treatment of refractory dermal melasma with the MedLite C6 Q-switched Nd:YAG laser: two case reports. J Cosmet Laser Ther. 2008;10:167–173.
13. Wattanakrai P, Mornchan R, Eimpunth S. Low-fluence Qswitched neodymium-doped yttrium aluminum garnet(1,064 nm) laser for the treatment of facial melasma in Asians. Dermatol Surg. 2010;36:76–87.
14. Cho SB, Kim JS, Kim MJ. Melasma treatment in Korean women using a 1064-nm Q-switched Nd:YAG laser with low pulse energy. Clin Exp Dermatol. 2009;34:e847–e850.
15. Mun JY, Jeong SY, Kim JH, Han SS, Kim IH. A low fluence Q-switched Nd:YAG laser modifies the 3D structure of melanocyte and ultrastructure of melanosome by subcellular-selective photothermolysis. J Electron Microsc. 2011;60:11–18.
16. Angsuwarangsee S, Polnikorn N. Combined ultrapulse CO2 laser and. Q-switched alexandrite laser compared with Qswitched alexandrite laser alone for refractory melasma: Split-face design. Dermatol Surg. 2003;29:59–64.
17. Wang CC, Hui CY, Sue YM, Wong WR, Hong HS. Intense pulsed light for the treatment of refractory melasma in Asian persons. Dermatol Surg. 2004;30:1196–1200.
18. Rokhsar CK, Fitzpatrick RE. The treatment of melasma with fractional photothermolysis: a pilot study. Dermatol Surg. 2005;31:1645–1650.
19. Li YH, Chen JZ, Wei HC, Wu Y, Liu M, Xu YY, et al. Efficacy and safety of intense pulsed light in treatment of melasma in Chinese patients. Dermatol Surg. 2008;34:693–700.
20. Lee HS, Won CH, Lee DH, An JS, Chang HW, Lee JH, et al. Treatment of melasma in Asian skin using a fractional 1,550-nm laser: An open clinical study. Dermatol Surg. 2009;35:1499–1504.
21. Kang WH, Yoon KH, Lee ES, Kim J, Lee KB, Yim H, et al. Melasma: Histopathological characteristics in 56 Korean patients. Br J Dermatol. 2002;146:228–237.
22. Chan HH, Xiang L, Leung JW, Tsang KW, Lai KN. An in vitro study examining the effect of sub- lethal QS 755 nm lasers on the expression of p16INK4a on melanoma cell lines. Lasers Surg Med. 2003;32:88–93.
23. Chan HH, Yang CH, Leung JC, Wei WI, Lai KN. An animal study of the effects on p16 and PCNA expression of repeated treatment with high-energy laser and intense pulsed light exposure. Lasers Surg Med. 2007;39:8–13.