

Efficacy and Safety Evaluation of Picosecond Alexandrite Laser with a Diffractive Lens Array for Treatment of Melasma in Asian Patients by VISIA Imaging System

Yu-Tsung Chen, MD,^{1,2} Erh-Ti Lin, MD,³ Chang-Cheng Chang, MD, PhD,^{3–6} Bor-Shyh Lin, PhD,⁴
Hsiu-Mei Chiang, PhD,⁵ Yung-Hsueh Huang, MD,⁷ Hui-Ying Lin, MS,⁸
Ke-Yi Wang, MS,⁵ and Tsong-Min Chang, PhD⁸

Abstract

Objective: To evaluate the efficacy and safety of picosecond (ps) 755-nm alexandrite laser with a diffractive lens array (DLA) generating laser-induced optical breakdown, which may be beneficial for melasma treatment.

Background: Melasma is notorious for difficult to treat with any modality setting. Recently, picosecond alexandrite laser with DLA seems promising for dealing with it without intolerable complications.

Methods: Twenty ($N=20$) Asian female melasma patients with Fitzpatrick skin type IV were recruited for 3 treatment sessions of picosecond 755-nm alexandrite laser with DLA at a 4- to 6-week interval. The pulse duration was 750 ps. An 8-mm spot size and the fluence of 0.4 J/cm^2 was used over the target area with 2 passes per treatment area and around 2000–2500 passes in total. The repetition rate was 10 Hz. Melasma Area and Severity Index (MASI) score and VISIA[®] imaging system analysis were utilized for evaluation before treatment and 4 weeks after the completion of the third treatment session. The clinical improvement and adverse events were assessed by the physicians and patients, respectively.

Results: The median age of the patients was 45 years (from 27 to 55 years). In the physicians' evaluation, 40% ($n=8$) of patients showed good improvement and 40% ($n=8$) of patients showed moderate improvement. The mean MASI score before and after laser therapy showed significant improvement from 9.0 ± 4.8 to 6.5 ± 3.7 ($p < 0.001$). VISIA analysis of the forehead presented significant improvement in spots ($p = 0.007$) and porphyrins ($p = 0.032$). Some patients experienced erythema (25%), pruritus (20%), and scaling (20%) but subsided within few days of using emollients and sunscreen. Only 5% ($n=1$) of patients developed mild postinflammatory hyperpigmentation, which also subsided in 3 weeks.

Conclusions: Three sessions of picosecond 755-nm alexandrite laser with a DLA were effective for melasma treatment in Asian patients with minimal side effects.

Keywords: melasma, picosecond, VISIA, alexandrite laser, diffractive lens array

Introduction

MELASMA IS COMMONLY found in Asian individuals with Fitzpatrick skin phototypes III through VI.¹ It has been reported at a higher prevalence in Southeast Asian population, in which 40% of females have melasma.² The facial

discoloration often leads to considerable psychological effects and impairment of patients' quality of life.³

It has been shown that Q-switched Nd:YAG laser, when operated in a sub-photothermolytic capacity, causes melanin granule dispersion and fragmentation without cellular destruction.^{4–7} However, the outcomes were inconsistent due

¹Department of Dermatology, Taipei Medical University Shuang Ho Hospital, Taipei, Taiwan (R.O.C.).

²School of Public Health, College of Public Health and Nutrition, Taipei Medical University, Taipei, Taiwan (R.O.C.).

³School of Medicine, College of Medicine, China Medical University, Taichung, Taiwan (R.O.C.).

⁴Institute of Imaging and Biomedical Photonics, National Chiao Tung University, Hsinchu, Taiwan (R.O.C.).

⁵Department of Cosmeceutics and Graduate Institute of Cosmeceutics, China Medical University, Taichung, Taiwan (R.O.C.).

⁶Aesthetic Medical Center, China Medical University Hospital, Taichung, Taiwan (R.O.C.).

⁷Yung-Hsueh Huang Dermatology Clinic, Changhua, Taiwan (R.O.C.).

⁸Department of Applied Cosmetology, Master's Program of Cosmetic Science, Hung Kuang University, Taichung, Taiwan (R.O.C.).

to the refractory and recurrent nature of melasma with different treatment modalities, including via oral, injection, or phototherapy, and adverse events such as postinflammatory hyperpigmentation (PIH), rebound hyperpigmentation, and postlaser hypopigmentation were often reported.^{8–11} In a randomized control split-face study, 18.2% (4/22) and 13.6% (3/22) of melasma patients developed rebound hyperpigmentation and hypopigmentation, respectively, on the Q-switched Nd:YAG laser-treated sites.¹⁰

A novel 755-nm picosecond (ps) alexandrite laser has shown promising results in tattoo and pigmented lesions removal.^{12,13} The evolutionary shortened pulse duration produces a photomechanical effect that results in fragmentation of tattoo ink and pigmentation.¹⁴ An innovative diffractive lens array (DLA) attached to the handpiece was developed to redistribute energy into high-fluence microbeams at fixed spot size, affecting up to only 10% of the treated area.¹⁵ Thus, the picosecond laser with a DLA seems to demonstrate more favorable safety profile.¹⁶ Within the focused high-fluence zone, laser-induced optical breakdown (LIOB) is created, characterized by intraepidermal vacuoles from the absorption of laser energy by melanin.¹⁷

The objective of this study was to evaluate the efficacy and safety of picosecond 755-nm alexandrite laser with a DLA on melasma in Asian patients.

Materials and Methods

From January 1, 2017, to December 31, 2017, patients who had sought treatment for unwanted facial pigmentation and consented to the treatment by picosecond 755-nm alexandrite laser device at a single dermatology center were enrolled in this study. Twenty healthy women ($N=20$) with Fitzpatrick skin type IV presenting with melasma (Fig. 1) and median age of 45 years (from 27 to 55 years) were recruited. The skin type was based on the dermatologist's determination.

Patients with skin wound without complete epithelialization, inflammation, or infection on the face from trauma, acne, or iatrogenic, or had systemic diseases that may possibly affect the face conditions, such as systemic lupus erythematosus, chronic kidney diseases, or liver diseases, were excluded. Patients who had received other cosmetic treatments, such as hydroquinone, kojic acid, arbutin, or tranexamic acid via topical or injection, and phototherapy, such as intense pulsed light and laser treatments, within a year before the enrollment were also excluded. We also

confirmed that none of the patients had a history of photosensitivity, abnormal scarring, or poor wound healing. The intake of oral contraceptive pills and the hormone replacement therapy were forbidden in a year before the enrollment and for the duration of the study period.

This prospective study was approved by the Institutional Review Board Ethical Committee of China Medical University Hospital (No. 105-REC1-135).

All pigmented lesions and the rest of the face were treated with picosecond alexandrite laser (PicoSure[®]; Cynosure, MA) with a DLA consisting of packed hexagonal lenses, which could deliver 70% of the total energy in <10% of the treated area per pass, and the remaining 30% of the energy would provide the low fluence in the background.¹⁵ Each patient received three treatment sessions at 4- to 6-week intervals. A 755-nm wavelength, 750-ps pulse duration alexandrite laser employing an 8-mm spot size, delivered at the average fluence of 0.4 J/cm², was utilized in this study. The target area would receive 2 passes per treatment area and around 2000–2500 passes in total. The repetition rate was 10 Hz (Table 1). This DLA is used to magnify and concentrate energy into microbeams to create LIOB in epidermis.¹⁵

The endpoint of each treatment session was mild erythema. Patients were asked to apply the same broad-spectrum sunscreens with sun protection factor 50+ (Cetaphil Daylong, SPF 50+, PA+++++) every 2–3 h during indoor and outdoor activities.

Objective and subjective assessments were conducted at the baseline and 4 weeks after the third session of the treatment. Standardized photographs were taken from the front and side of both cheeks using VISIA[®] (Canfield Scientific, Inc.) Complexion Analysis imaging system with standardized fluorescent light and background, and all camera parameters were fixed with fixed angle, flash, and distance.

Clinical improvement was categorized as mild (<25% improvement), moderate (25–50% improvement), good (50–75% improvement), and excellent (>75% improvement) compared with the baseline by both physicians and patients. The changes in the severity of melasma before and after laser therapy were compared using the Melasma Area and Severity Index (MASI) score, which was developed and validated for quantification of severity of melasma and change during therapy.¹⁸

The total MASI score was calculated by multiplying the percentage of involved area (A) with the sum of darkness (D) and homogeneity (H) as given in the formula: $MASI\ score = 0.3Af \times (Df + Hf) + 0.3Arm \times (Drm + Hrm) + 0.3Alm \times$

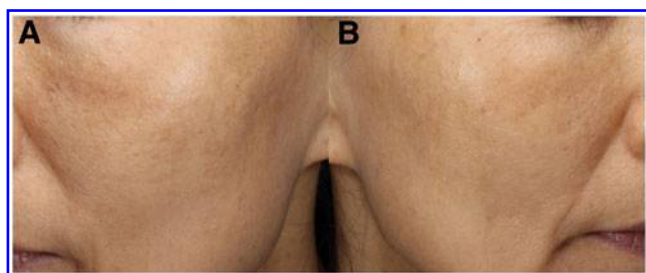


FIG. 1. Classic melasma. This 50-year-old female presented with symmetrically distributed brown to dark macules in both malar regions with irregular margin. (A) Left malar region. (B) Right malar region.

TABLE 1. THE PARAMETERS AND SETTINGS IN THIS STUDY

Pulse duration	750 ps
Wavelength	755 nm
Spot size	8 mm
Fluence	0.4 J/cm ²
Number of passes per treatment area	2 passes
Repetition rate	10 Hz
Total passes per treatment	2000–2500 passes
Interval	4–6 weeks
Diffractive lens array	Equipped

ps, picosecond.

(D_{lm} + H_{lm}) + 0.1Ac × (D_c + H_c), where “f” indicated “forehead,” “rm” indicated “right malar region,” “lm” indicated “left malar region,” and “c” indicated “chin”; the coefficient in front of the percentage of involved area indicated the proportion of the anatomical area of the whole face (f: 30%, rm: 30%, lm: 30%, and c: 10%). The area involved (0=no involvement, 1=<10%, 2=10–29%, 3=30–49%, 4=50–69%, 5=70–89%, 6=90–100%) as well as the darkness and homogeneity (0=absent, 1=slight, 2=mild, 3=marked, 4=severe) of pigmentation was scored from 0 to 4. The lower MASI score indicated less severe melasma.

Two blinded independent physicians (one dermatologist and one plastic surgeon, respectively) performed the evaluation of the clinical photographs before and after laser therapy to determine the degree of clinical improvement, the MASI score, and the presence of any complications from the photographs taken from VISIA imaging system. The consensus was made by two physicians if there are different degrees of area, darkness, or homogeneity of melasma.

Patients were also asked to self-evaluate the degree of improvement with the same scale rated as mild, moderate, good, and excellent. Before and after laser therapy, an objective assessment was evaluated by using VISIA (Canfield Scientific, Inc.) Complexion Analysis imaging system using its own database under the same light setting, which included eight parameters including spots, wrinkles, texture, pores, ultraviolet (UV) spots, brown spots, red areas, and porphyrins on the forehead and both cheeks. A higher VISIA score indicated better skin condition.

Statistical analysis

Data analysis was performed by using the SPSS Statistics (version 21; IBM, Armonk, NY) software. The Wilcoxon signed-rank test was used to examine the improvement of MASI and VISIA scores after treatment. Linear regression was used to analyze the relation between the MASI score at baseline and its improvement. *p*-Value of <0.05 was considered statistical significant.

Results

The median age of the patients was 45 years (from 27 to 55 years). Forty-five percent (*n*=9) of patients self-scored good improvement, whereas 25% (*n*=5) and 30% (*n*=6) of patients self-scored moderate and mild improvement, respectively. In the physicians' evaluation, 40% (*n*=8) of patients showed good improvement, whereas 40% (*n*=8) and 20% (*n*=4) of patients showed moderate and mild improvement, respectively (Table 2). The representative photographs of good improvement are shown in Figs. 2 and 3.

The distribution of the MASI scores of 20 patients before and after treatments showed clear tendency of reduction (Fig. 4). The mean MASI score of 20 patients was 9.4 ± 4.7 at baseline, which improved significantly to 6.9 ± 3.7 after 3 sessions of picosecond laser therapy (*p*<0.001). More detailed data showed that there were significant improvements on the darkness and homogeneity across right malar region, left malar region, and chin (Table 3). However, significant reduction of the targeted area was only noted in chin (*p*=0.042). In the linear regression model (Fig. 5), the MASI improvement after the treatment is moderately to

TABLE 2. PATIENTS' CHARACTERISTICS AND CLINICAL IMPROVEMENT

Number	20
Age, years, mean ± SD	43.75 ± 8.15
Female, <i>N</i> (%)	20 (100)
Clinical improvement vs. Baseline	
Patient's self-evaluation, <i>n</i> (%)	
Mild	6 (30)
Moderate	5 (25)
Good	9 (45)
Excellent	0
Physician's evaluation, <i>n</i> (%)	
Mild	4 (20)
Moderate	8 (40)
Good	8 (40)
Excellent	0

Mild: <25% improvement; moderate: 25–50% improvement; good: 50–75% improvement; excellent: >75% improvement. Baseline, before treatment; SD, standard deviation.

strongly correlated with the MASI score at baseline (*r*=0.66, *p*=0.002).

The VISIA analysis showed improvement on the forehead after picosecond laser therapy, although only spots (*p*=0.007) and porphyrins (*p*=0.032) were markedly improved. In both malar regions, VISIA analysis showed significant improvement in UV spots (*p*=0.044), brown spots (*p*=0.017), and porphyrins (*p*=0.02) (Table 4).

Only minor anticipated adverse events were observed during the treatment (Table 5). Some patients experienced

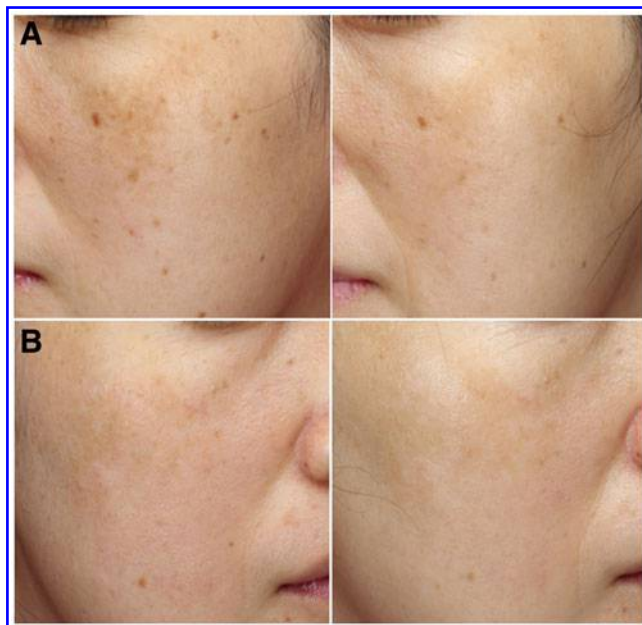


FIG. 2. Patient with melasma before and after treatment with 755-nm picosecond alexandrite laser. A 43-year-old female with melasma and solar lentigo showed good improvement (grading by both patient and physicians) after treated with picosecond 755-nm alexandrite laser with diffractive lens array 4 weeks after the third treatment session. (A) Left cheek at baseline (upper left) and after the treatment (upper right). (B) Right cheek at baseline (lower left) and after the treatment (lower right).

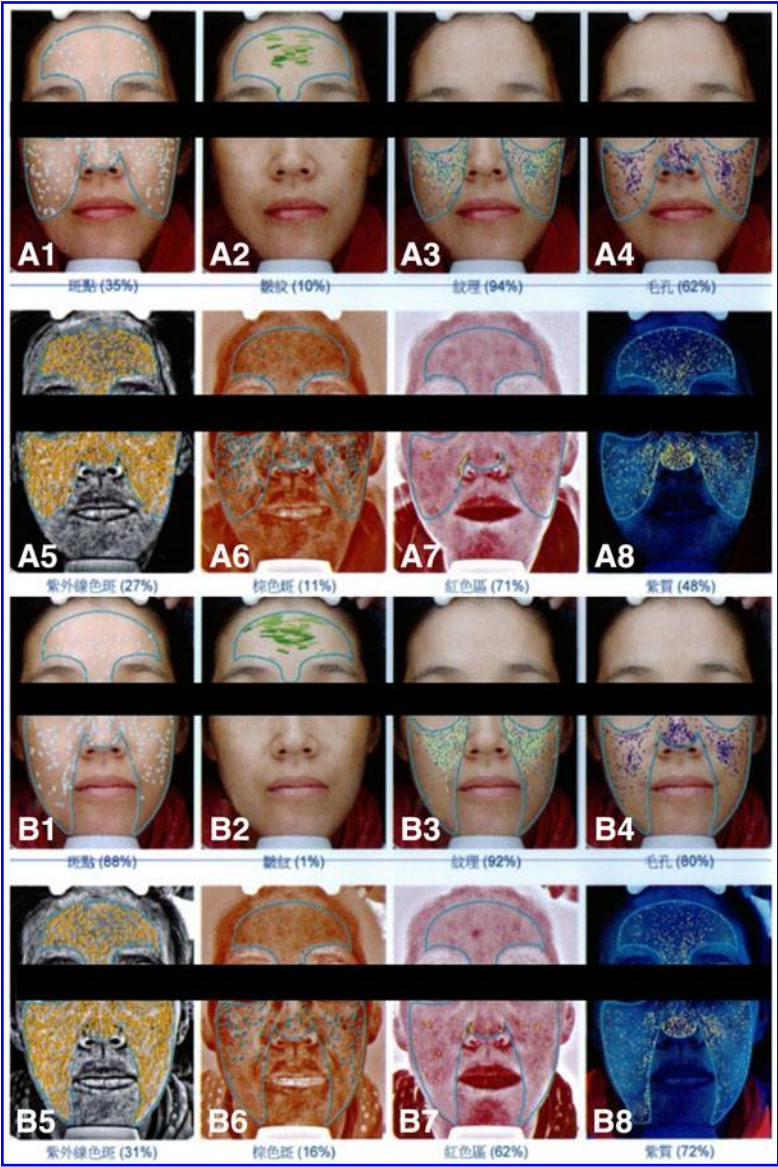


FIG. 3. Evaluation using VISIA image system. The 43-year-old female with melasma was evaluated by VISIA imaging system. Spots, pores, and porphyrins were markedly improved after the picosecond alexandrite laser therapy (A). At baseline (B) after three laser treatment sessions (1) spots, (2) wrinkles, (3) textures, (4) pores, (5) UV spots, (6) brown spots, (7) red areas, and (8) porphyrins. UV, ultraviolet.

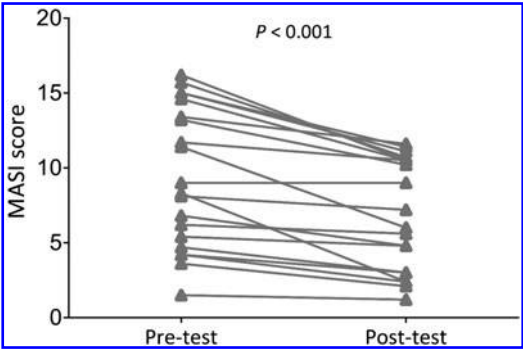


FIG. 4. Distribution of the MASI score before and after intervention. The mean MASI score of 20 patients was 9.4 ± 4.7 at baseline, which improved significantly to 6.9 ± 3.7 ($p < 0.001$) after 3 sessions of picosecond laser therapy. MASI, Melasma Area and Severity Index.

erythema (25%), pruritus (20%), and scaling (20%), which subsided within few days of usage of emollients and sun-screen. Only one patient (5%) developed mild PIH, which was relieved within 3 weeks.

Discussion

Picosecond lasers can produce high energy to enhance the photomechanical effect and reduce thermal injury to the surrounding tissues.¹⁴ Such a therapeutic mode results in more selective to fragmented melanin granules and thus may reduce adverse events (e.g., PIH) and shorten treatment duration as well as the number of treatment sessions in the management of melasma. The formation of LIOB with the DLA can enhance subsequent laser irradiation, meanwhile preventing dermoepidermal junction from excessive radiation and minimizing collateral thermal damages to the surrounded area.¹⁹

Therefore, a picosecond laser with a DLA demonstrates a more favorable safety profile than a picosecond laser with a

TABLE 3. MELASMA AREA AND SEVERITY INDEX SCORES BEFORE AND AFTER LASER THERAPY

	Before	After	p*
Forehead (f)			
Area	0.70 ± 0.80	0.70 ± 0.73	1.000
Darkness	0.80 ± 0.95	0.70 ± 0.86	0.163
Homogeneity	0.90 ± 1.12	0.70 ± 0.73	0.214
Right malar region (rm)			
Area	2.40 ± 0.88	2.10 ± 0.79	0.055
Darkness	2.90 ± 0.91	2.30 ± 0.92	<0.001
Homogeneity	2.65 ± 0.99	2.05 ± 0.83	<0.001
Left malar region (lm)			
Area	2.35 ± 0.75	2.25 ± 0.79	0.494
Darkness	2.75 ± 0.97	2.20 ± 1.01	<0.001
Homogeneity	2.45 ± 0.94	2.15 ± 0.88	0.030
Chin (c)			
Area	0.45 ± 0.51	0.25 ± 0.44	0.042
Darkness	0.55 ± 0.69	0.30 ± 0.57	0.021
Homogeneity	0.65 ± 0.99	0.35 ± 0.75	0.010
MASI score	9.4 ± 4.7	6.9 ± 3.7	<0.001

Data are expressed as mean ± SD.

* $p < 0.05$ indicated significant difference.

MASI, Melasma Area and Severity Index.

TABLE 4. VISIA ANALYSIS BEFORE AND AFTER LASER THERAPY

	Before	After	p*
Forehead			
Spots	42.3 ± 26.0	57.8 ± 29.7	0.007
Wrinkles	38.6 ± 24.0	41.0 ± 32.7	0.675
Texture	70.7 ± 26.5	77.1 ± 21.0	0.250
Pores	57.6 ± 36.1	72.6 ± 26.4	0.092
UV spots	40.2 ± 21.9	43.9 ± 23.7	0.097
Brown spots	22.9 ± 26.7	26.3 ± 27.9	0.091
Red areas	45.4 ± 20.9	33.7 ± 21.2	0.060
Porphyryns	61.6 ± 37.2	81.1 ± 14.6	0.032
Mean of both cheeks			
Spots	77.7 ± 22.7	85.8 ± 14.5	0.138
Wrinkles	49.4 ± 25.3	57.9 ± 22.8	0.080
Texture	81.9 ± 17.6	83.6 ± 18.7	0.412
Pores	69.0 ± 25.6	75.6 ± 21.0	0.341
UV spots	34.5 ± 23.8	44.3 ± 23.2	0.044
Brown spots	41.3 ± 18.9	49.3 ± 22.3	0.017
Red areas	49.3 ± 17.4	43.8 ± 25.9	0.437
Porphyryns	64.7 ± 28.7	82.6 ± 10.7	0.020

Data are expressed as percentage ± SD.

* $p < 0.05$ indicated significant difference.

UV, ultraviolet.

holographic optic and Q-switched nanosecond laser.^{16,20} In our study, patients (all with Fitzpatrick skin type IV) treated with 755-nm picosecond laser with a DLA only experienced transient adverse events, which were subsided within a few days. The mild PIH developed in one patient also subsided within 3 weeks. No exfoliation, vesiculation, crusting, scarring, hypopigmentation, or hyperpigmentation was observed during the study period.

Melasma is considered a female hormone-related disease with a genetic predisposition.^{21–24} Histological examination of skin with melasma demonstrates evidence of increased

activity of melanogenesis, including enlarged melanocytes with prominent dendritic processes, increased epidermal melanin content, and slightly increased number of dermal melanophages.^{25–27}

However, in the past decade, histological studies showed that melasma was more than hyperactivity of melanocytes, but a photoaging skin disorder with increased solar elastosis, dermal mast cells, and vascularization.^{24,26,28–30} The expression of vascular endothelial growth factor, which increases melanogenesis via the arachidonic acid pathway, is upregulated in melasma.²⁹ Endothelial cells were also found to stimulate pigmentation through the production of endothelin 1.³⁰ The formation of LIOB by picosecond laser with a DLA not only stimulates an epidermal repair mechanism but also leads to more stable melasma based on the analysis of digital images in this study.¹⁷ We believe that the improvement of the MASI score is associated with the above mechanisms rather than merely the direct results of melanin destruction.

In our study, pigmentation disorder in forehead generally showed no improvement in area, darkness, and homogeneity. This may result from several factors. The condition before the therapy was not severe enough that the improvement was hard to measure in clinical practice. Also,

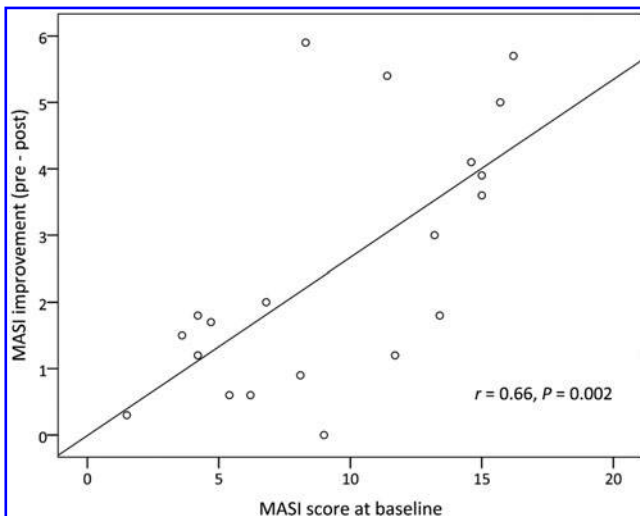


FIG. 5. Relationship between the MASI score at baseline and the improvement of the MASI score. The MASI score at baseline was moderately to strongly related to its improvement after treatment ($r = 0.66$, $p = 0.002$), which suggested that patients with severe melasma could highly profit from this treatment modality.

TABLE 5. EXPERT-REPORTED POSTLASER SIDE EFFECTS

	N (%)
Erythema	5 (25)
Dryness	1 (5)
Pruritus	4 (20)
Scaling	4 (20)
PIH	1 (5)

N, number of reported patients; PIH, postinflammatory hyperpigmentation.

forehead could get more sun exposure than the rest of the face. More passes per treatment in this area may be needed for better outcomes.

Previous studies have confirmed that picosecond 532- and 1064-nm Nd:YAG laser with a holographic optic caused more vascular damage and subsequent cutaneous hemorrhaging than the 755-nm picosecond laser with a DLA.²⁰ The vascular damage could further result in inflammatory changes and melanogenesis and thus increase the incidence of PIH.³¹ The only Food and Drug Administration-approved laser treatment for melasma is fractional photothermolysis, which creates microscopic treatment zones of thermal injury to the dermis and epidermis.³² Unlike the conventional nanosecond or fractional photothermolysis laser, the LIOB generated by the 755-nm picosecond laser with a DLA is limited within epidermis, leaving only subtle thermal damage to the dermis below.

By using the VISIA image system, we also observed the improvement in skin condition in pigmentation sites or uninvolved areas, the spots, UV spots, brown spots, and porphyrins in particular. The reduction of spots and brown spots indicates the decrease in hyperpigmentation and discoloration, whereas the lightening of UV spots suggests less melanin deposition as a result of sun damage.

A split-face study demonstrated a superior clearance rate of 755 nm alexandrite picosecond laser for melasma compared with the 1064 nm QS-Nd:YAG laser.³³ *Propionibacterium acnes* produces porphyrin, which can exhibit fluorescence properties under long-wavelength UVA radiation.³⁴ Porphyrin has phototoxicity that induces oxidative stress to the lipids and proteins, leading to skin inflammation and damages.^{35–37} Thus, the reduction of porphyrin production theoretically reduces skin damages. The reduction in porphyrin may be due to the altered epidermal environment, which usually accelerates the transport of melanosomes and epidermal metabolism, but the exact reason was not clearly understood and thus need more evidence to clarify the phenomena.

Previous studies reported that picosecond lasers significantly reduced wrinkles and improved photodamage, which is one of the predisposing factors of melasma recurrence.^{38–40} The mechanism is unclear yet, and it is proposed to be associated with the production of new collagen and the changes in cell signaling.^{15,41–44} The area where LIOB react would form vacuoles and cavitation, then collapse, and generate local mechanical forces that could further disrupt surrounding tissues and propagate to the dermis, leading to barotrauma and results in dermal remodeling, and finally reduces vascularization and inflammation.⁴⁴ It has been postulated that pressure waves temporarily enhance cellular membrane permeability, altering cell signaling and initiating a cytokine cascade for dermal improvement.^{43,44}

Keratinocytes release growth factors, cytokines, and chemokines after in response to injury, which further stimulate and regulate the response to LIOB.⁴⁵ Although histological examination was not performed in this study, our observation by VISIA indirectly indicated that picosecond 755-nm alexandrite laser with a DLA not only improved the pigmentation and reduced inflammatory vasculature but also repaired the epidermis and dermis through the above mechanisms. In brief, based on our VISIA data, the underlying photodamaged aging skin caused by melasma

was improved when treated with a picosecond laser with a DLA.

This study had a short follow-up period and lacked a gender-matched control group, and no subgroup analysis was made. Most patients had mild-to-moderate melasma, which may bias the outcome assessment. However, the objective assessment using VISIA image analysis showed significant improvement in skin conditions. PIH may appear 4 weeks after laser treatment, and a 4 week follow-up may not be sufficient to confirm the outcome of treatment. Furthermore, lack of control and sunscreen itself may account for clinical improvement in melasma. Further randomized controlled trial with longer follow-up period is needed. Skin biopsies for histological analysis would be also required, but with difficult compliance.

Conclusions

This pilot study demonstrated the efficacy and safety profile of the picosecond 755-nm alexandrite laser with a DLA in melasma patients with Fitzpatrick skin type IV. In addition to the improvement of melasma, such laser therapy also improved skin conditions. However, the MASI improvement in forehead was not observed, and it may be due to several reasons in this study. No serious adverse events were observed. Picosecond 755-nm alexandrite laser with a DLA could be a suitable treatment modality for melasma in addition to the Q-switched laser.

Acknowledgments

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Author Disclosure Statement

No competing financial interests exist.

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Address correspondence to:
Chang-Cheng Chang, MD, PhD
Aesthetic Medical Center
China Medical University Hospital
Taichung 404
Taiwan (R.O.C.)

E-mail: changcc1975@gmail.com

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