

Photoaging Reversibility in Asian Patients With Melasma Treated Using Picosecond Lasers With Diffractive Lens Array: A 1-Year Prospective Observational Cohort Study

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BACKGROUND Picosecond lasers appear to be effective and safe in treating pigmentation and photoaging disorders through laser-induced optical breakdown.

OBJECTIVE To analyze the feasibility of photorejuvenation using picosecond lasers with diffractive lens array (DLA) in patients with melasma.

METHODS Ten Asian ($N = 10$) women with melasma and Fitzpatrick skin Type IV were enrolled and treated using 755-nm picosecond alexandrite lasers with DLA. All individuals were assessed before treatment, and at 12, 20 weeks, and 1 year by *post-hoc test* on melasma area and severity index (MASI) and with VISIA Complexion Analysis System using percentile rank for measurement.

RESULTS The median participant age was 46.5 years. The average MASI continually and significantly ($p < .05$) decreased until the 1-year follow-up, with the photoaging characteristics, such as wrinkles and red areas improving simultaneously ($p < .05$). Spots, texture, pores, ultraviolet (UV) spots, brown spots, and porphyrins exhibited alleviation, but this improvement relapsed by the 1-year follow-up. No postinflammatory hyperpigmentation or hypopigmentation occurred.

CONCLUSION In patients with melasma, picosecond laser treatment with DLA may alleviate pigmentation disorder and the related photoaging characteristics (e.g., wrinkled skin and increased vascularity), and the effects may be maintained for a long time. Nevertheless, post-treatment clinical visits every 3 to 6 months are recommended.

This study was funded by the Clinical Trial Center of Taiwan Ministry of Health and Welfare (MOHW 106-TDU-B-212-113004) and the China Medical University Hospital (DMR-106-036). The authors have indicated no significant interest with commercial supporters.

Melasma, a pigmentation disorder frequently noted in Asian populations,¹ is characterized by light to dark brown irregular macules with symmetrical spread on the face. Although asymptomatic, the disfiguring disorder can significantly affect the quality of life,² and persistent deterioration is one of its undesirable characteristics. Melasma generally results from genetic predisposition

or hormonal stimulation; it can also be caused by a photoaging skin disorder³ characterized by solar elastosis, damaged basement membrane allowing deposition of melanin,⁴ defragmented dermal collagens, and increased vascularization.⁵

Melasma treatment remains challenging because of inconsistent treatment results with frequent relapses.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.dermatologicsurgery.org).

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ISSN: 1076-0512 • Dermatol Surg 2020;00:1–6 • DOI: 10.1097/DSS.0000000000002405

Lasers are a promising therapeutic modality and are adopted for treating dermatologic conditions. Low fluence Q-switched neodymium-doped yttrium aluminum garnet lasers can be used to effectively treat melasma through selective photothermolysis of melanosomes^{6,7}; however, mottled hypopigmentation may occur in a few patients because of impaired melanogenic activity in melanocytes.⁸ Nonablative fractional lasers, which facilitate dermal melanophagocytosis, are also indicated for melasma treatment,⁹ but their common short-term adverse effects include erythema, swelling, and pain, and postinflammatory hyperpigmentation (PIH) is also reported.¹⁰

With the innovations in laser designs and the recent development of device available for picosecond-domain pulse duration, it permits pigment fragmentation to be more a result of photoacoustic effects, rather than photothermal effects. Picosecond lasers reveal breakthrough outcomes in tattoo pigment clearance with low incidence of adverse effects.¹¹ Furthermore, picosecond lasers proceed with the extensive applications in diverse dermatologic conditions beyond pigment removal to acne scarring, photoaging, and more. In addition to the ultra-short pulse duration, diffractive lens array (DLA) contributes to the decreased amount of unfavored adverse effects by evenly dispersing the energy in pixel arrangement.^{12,13}

Pertaining to quantitative tools, melasma area and severity index (MASI) is a reliable measurement between raters¹⁴; moreover, VISIA automatic skin analysis system demonstrates an acceptable correlation in measuring various skin conditions¹⁵ using general lights and UV/cross-polarized lights.

We hypothesize that the photoaging characteristics of melasma could be reversed by the effect of laser-induced optical breakdown (LIOB) and maintained through dermal remodeling. This study analyzes the feasibility and efficacy of photorejuvenation and long-term maintenance in Asian individuals with melasma receiving treatment with picosecond lasers with DLA and with valid assessment.

Materials and Methods

This is a prospective observational cohort study conducted in a single tertiary referral center. 755-nm picosecond alexandrite lasers with a DLA were used for reversing pigmentation and photoaging disorders in Asian individuals with melasma. Each patient received several treatment sessions (3–5) of laser therapy at 4-week intervals. MASI and an automatic skin analysis system were adopted for measurement before the treatment and at 12, 20 weeks, and 1 year after the initial treatment. All the adverse effects related to laser therapy such as redness, dryness, PIH, hypopigmentation, itchiness, and desquamation were recorded. The study was approved by the Research Ethics Committee of the China Medical University and Hospital (CMUH107-REC1-152).

Patients

From March 2017 to June 2018, 10 Asian individuals ($N = 10$, all women) with Fitzpatrick skin Type IV and presenting with mixed type melasma were enrolled. All lived in central Taiwan in the subtropical zone and had a median age of 46.5 years (from 34 to 55 years). All agreed to long-term follow-up. Skin types were determined by the investigator.

Individuals with histories of pharmacologic treatment with depigmenting agents such as hydroquinone, tretinoin, azelaic acid, steroids, kojic acid, and pido-benzene; of tranexamic acid usage; of hormone replacement therapy; of chemical peels; or of any phototherapy modalities within 1 year before the study were excluded. In addition, individuals with histories of skin photosensitivity, hypertrophic scars, or impaired wound healing were excluded.

All participants' histories were carefully examined, and informed consent was acquired before the study began. To prevent possible bias, all individuals were instructed to use the same broad-spectrum sunscreen with sun protection factor 50+ and protection grade of ultraviolet (UV) A band ++++ (Daylong, Cetaphil; TX) and the same baby moisturizers (Cetaphil) every 2 hours during daytime and to minimize sun exposure throughout the study period.

Seven Hundred Fifty-Five Nanometer Picosecond Alexandrite Lasers With Diffractive Lens Array

Seven hundred fifty-five nanometer picosecond Alexandrite lasers (PicoSure; Cynosure, Westford, MA) with a DLA were used. The spot size was 8-mm. The pulse duration was 750-ps. The frequency was 10 Hz. The fluence was 0.4 J/cm² with 2 passes performed in the same area and with a total count of approximately 2,500 passes each time. The end point of each laser treatment was mild erythema without petechiae. Five percent lidocaine cream (Lidiprine; cBc, Taiwan) was topically applied approximately 40 minutes before the treatment for pain reduction. After laser therapy, skin was cooled for 15 minutes with icepacks.

Melasma Area and Severity Index

Melasma area and severity index was calculated by multiplying the percentage of affected areas (A) by the summation of the darkness (D) and the homogeneity (H) as given by the formula: $0.3 \times A_F \times (D_F + H_F) + 0.3 \times A_{RM} \times (D_{RM} + H_{RM}) + 0.3 \times A_{LM} \times (D_{LM} + H_{LM}) + 0.1 \times A_C \times (D_C + H_C)$. Among the formula, “F” represents “forehead,” “RM” represents “right malar region,” “LM,” represents “left malar region,” and “C” represents “chin.” The coefficient indicated proportions in relation to the whole facial area: the forehead accounted for 30%, the right malar region accounted for 30%, the left malar region accounted for 30%, and the chin accounted for 10%. The areas were scored from 0 to 6 (0 = unaffected, 1 = <10%, 2 = 10%–29%, 3 = 30%–49%, 4 = 50%–69%, 5 = 70%–89%, 6 = 90%–100%). The darkness and the homogeneity of pigmentation were scored on a scale from 0 to 4 (0 = absent, 1 = slight, 2 = mild, 3 = marked, and 4 = severe). The total MASI was between 0 and 48, and a higher index indicated more severe melasma.

Two physicians (one plastic surgeon and one dermatologist) independently measured the score from the digital images captured by an automatic skin analysis system. If discrepancies occurred between their analyses of percentages for the affected areas and the

measurements of darkness and homogeneity, then both physicians would conduct reassessments until a consensus was reached.

Automatic Skin Analysis System

Automatic skin analysis system (VISIA Complexion Analysis System; Canfield Scientific, Inc., Parsippany-Troy Hills, NJ) was used to objectively evaluate facial skin conditions, including spots, wrinkles, texture, pores, UV spots, brown spots, red areas, and porphyrins according to percentile rank, the scores for which range from 0 to 99 using its database to assign grades and compare them with those for the skin of other individuals of the same age. The distance and angle of the camera was fixed. Multispectral imaging was captured with standardized light, cross-polarized flash, and ultraviolet lighting.

Statistics

Continuous data were presented as mean \pm SD. Values of the skin analysis system among the different follow-ups were compared using generalized estimating equation where the main effect of time period was the only explanatory variable and by running *post-hoc test*. A 2-sided *p*-value < .05 was considered statistically significant and no adjustment of multiple testing (multiplicity) was made in this study. Data analyses were conducted using SPSS 22 (IBM SPSS, Inc., Chicago, IL). Melasma improvement rate was defined as the difference between the MASI at the time of the assessment and the baseline divided by the MASI of the baseline.

Results

Among all participants (See **Supplemental Digital Content 1**, Table S1, <http://links.lww.com/DSS/A311>), 4 of them received 3 times of laser therapy sessions, and 6 of them received 5 sessions. MASI was significantly reduced from 9.24 ± 4.81 (mean \pm SD) before the treatment, to 6.65 ± 3.31 with an improvement rate of 28% at 12 weeks, to 5.61 ± 3.16 with an improvement rate of 39% at 20 weeks, and to 5.73 ± 2.88 with an improvement rate of 38%

at 1-year follow-up (See **Supplemental Digital Contents 2 and 3**, Figure S1 and Table S2, <http://links.lww.com/DSS/A312> and <http://links.lww.com/DSS/A313>, respectively). Although the MASI regressed at 1 year compared with that at 20 weeks for half of the patients, all still exhibited improvement compared with that before treatment.

According to the skin analysis system (See **Supplemental Digital Content 3**, Table S2, <http://links.lww.com/DSS/A313>), spots had significantly alleviated at 12 weeks and at 20 weeks compared with before treatment, but this improvement relapsed by the 1-year follow-up compared with that at 20 weeks on the MASI. Wrinkles significantly improved at 1-year follow-up compared with before treatment (See **Supplemental Digital Content 4**, Figure S2, <http://links.lww.com/DSS/A314>). Texture exhibited minimal change during the treatment and at the 1-year follow-up. Pores had improved at 12 weeks and at 20 weeks compared with before the treatment, but had regressed by the 1-year follow-up (See **Supplemental Digital Content 5**, Figure S3, <http://links.lww.com/DSS/A315>). In the analysis under UV/cross-polarized lights, UV spots, and porphyrins had both improved, but regressed by the 1-year follow-up. Brown spots had significantly improved at 12 weeks compared with before treatment, but had regressed at 20 weeks. Red areas, however, had markedly improved by the 1-year follow-up.

Overall, 20% of the patients developed mild erythema, 20% developed itchiness, and 40% developed desquamation after treatment, all of which subsided after a few days to a few weeks. No PIH or hypopigmentation occurred.

Discussion

The adoption of lasers in treating pigmentation disorders is based on the theory that the specific spectrum of lights emitted by a particular type of laser would be selectively absorbed by the targeted cells or tissues, which is known as process of selective photothermolysis.¹⁶ The invention of sub-nanosecond laser represents a new era of precise photomechanical

effects, and these lasers are usually far stronger than those created from ablation based on linear absorption.¹⁷ In a prospective study, potassium titanyl phosphate (KTP) 532-nm picosecond lasers resulted in significantly higher satisfaction for patients with solar lentigines compared with Q-switched KTP 532-nm nanosecond laser.¹⁸ To avoid risks of cutaneous hemorrhage and to shorten period of skin erythema, 755-nm wavelength was preferable than 532- or 1064-nm fractional picosecond device.¹⁹ In our study, picosecond lasers demonstrated adequate efficacy for treating melasma with photoaging characteristics even in a 1-year duration. By absorbing the highly intensified laser beams created by the special lens, the irradiated regions of the skin rapidly heat up above boiling temperature of the surrounding tissues and form vacuoles in the epidermis,¹³ which we believe to be the key role in reducing pigment and inducing neocollagenesis.

Severity of melasma mildly regressed at 1 year compared with that at 20 weeks in half of the patients in our research. Relapse remained a challenge. Nevertheless, marked improvement in MASI at 1 year compared with before the laser treatment was noted.

The 755-nm picosecond alexandrite lasers equipped with DLA have been documented as safe and effective for the treatment of photoaging features including wrinkles in recent years. In our study, both wrinkled skin and red areas exhibited improvement even at 1-year follow-up (See **Supplemental Digital Content 4**, Figure S2, <http://links.lww.com/DSS/A314>). Although the location of the LIOB caused by 755-nm picosecond lasers was mainly melanin in the epidermis,¹³ the process may generate shock waves, disrupt the surrounding tissues and activate the repair response.²⁰ With the collagen remodeling, we speculate that the disrupted basement membrane in melasma may be restored, which is essential to the long-term effects. Additional improvement in red areas, in our opinion, is attributed to the amelioration of the chronic inflammation status. However, more studies are needed to confirm the treatment consistency and the exact mechanism underlying photoaging reversibility.



Figure 1. Fine wrinkles and pigmentation disorders continually improved and the effects were maintained well after 3 sessions of picosecond laser treatment in a 48-year-old woman (#1). (A) Forehead before the treatment (B) forehead at 1-year follow-up (C) left malar region before the treatment; and (D) left malar region at 1-year follow-up.

Spots and pores generally demonstrated a trend of improvement and then regression without further treatment (See **Supplemental Digital Content 5**, Figure S3, <http://links.lww.com/DSS/A315>) as similar as MASI analysis (See **Supplemental Digital Content 2**, Figure S1, <http://links.lww.com/DSS/A312>). Texture exhibited minimal change during treatment and at the 1-year follow-up. However, many factors including direct UV exposure, and friction from daily activity could possibly affect the superficial layer. Therefore, to maintain efficacy in the superficial layer of the skin, such as for spots, texture, and pores, repeated treatment may be required with facial care instructions.

Epidermal melanin and porphyrins exhibited fluorescence under UV light exposure.²¹ Phototoxicity of porphyrins would cause inflammation in the skin and subsequent damage.²² Both UV spots and porphyrins improved with the picosecond laser treatment until the 20th week and then mildly regressed at 1 year. Although the picosecond lasers with DLA in our setting had smooth operation without intolerable adverse effects, we nonetheless recommended regular visits to clinics every 3 to 6 months and offered repeated treatment using pico-

second lasers with a DLA, further recommendations for sunscreen use, and monitoring of skin conditions.

To observe photoaging reversibility and maintenance of treatment effects by picosecond alexandrite laser with a DLA, the patients were evaluated 1 full year after the initial therapy (Figures 1 and 2). Thus, in our opinion, the photoaging reversibility and maintenance was because of the reaction induced by the picosecond laser with DLA rather than seasonal effects. Notably, one study demonstrated that applying broad spectrum sunscreen every day may also reverse the signs of photodamage in a one-year prospective study.²³

Few adverse effects, such as desquamation, erythema, and itchiness occurred within a few days to a few weeks after the laser therapy, and no PIH or hypopigmentation occurred in this study.

Limitation

Our study has several limitations. The study size was small because of the difficulties in compliance regarding long-term follow-ups. Skin biopsy was not performed because of personal cosmetic concerns. Patients received



Figure 2. Pigmentation along with fine wrinkles and red areas continually improved and the effects were maintained well after 5 sessions of picosecond laser treatment in this 43-year-old woman (#9). (A) Forehead before the treatment (B) forehead at 1-year follow-up (C) left malar region before the treatment; and (D) left malar region at 1-year follow-up.

various treatment sessions, which may possibly have affected the assessment result especially at 20 weeks. The same sunscreen and moisturizer were applied during the study, but data regarding their use among patients before treatment were unavailable, which may also have influenced the severity of melasma. Nonetheless, our study demonstrated photorejuvenation effects and potential for maintenance up to 1 year with objective analysis.

Conclusions

Continual picosecond laser therapies with DLA at 4-week intervals could potentially reverse pigmentation disorder with photoaging characteristics, such as wrinkled skin and increased vascularity without intolerable adverse effects, and this may also be maintained in some patients. The melasma of half of the patients in our study mildly regressed after 6 months without laser therapy. Regular visits to the clinics every 3 to 6 months are recommended.

Acknowledgments The authors thank Dr. Joe Chi-Cheng Fang of Greenslopes Private Hospital, Australia, for his assistance in editing the manuscript. The authors thank Alfred Hsing-Feng Lin, a biostatistician from Raising Statistics Consultant Inc., for his statistical assistance during the completion of this manuscript.

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