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**Prospective Randomised Controlled Trial Comparing Treatment Efficacy and
Tolerance of Picosecond Alexandrite Laser with a Diffractive Lens Array and Triple
Combination Cream in Female Asian Patients with Melasma**

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Abstract

Background: Recent evidence suggests melasma to be a photoaging disorder. Triple combination creams (TCC; fluocinolone acetonide 0.01%, hydroquinone 4%, and tretinoin 0.05%) remain the gold standard treatment. Picosecond alexandrite laser treatment using a diffractive lens array (DLA) has been identified to be effective for improving photoaging conditions.

Objective: We aimed to compare the efficacy and tolerance of the picosecond alexandrite laser with those of DLA and TCC in female Asian patients with melasma.

Methods: Twenty-nine patients were randomly assigned to group A1 (3 laser sessions at 4-week intervals), A2 (5 laser sessions at 4-week intervals), or B (TCC daily for at least 8 weeks and then tapered until the final evaluation). The Melasma Area, Severity Index (MASI) score and VISIA were assessed at baseline, week 12, and week 20. By week 20, the follow-up periods for groups A1 and A2 were 3 months and 1 month, respectively.

Results: Nine, 11, and 6 participants in groups A1, A2, and B completed the study, respectively. MASI scores were significantly improved in all 3 groups at weeks 12 and 20. In groups A1, A2, and B, the improvement rates at week 20 were 53%, 38%, and 50%, respectively. VISIA® analysis additionally revealed a significant improvement in spots, porphyria, pores, and brown spots after 3 laser sessions ($p<0.05$). Group A2 showed greater improvements than group A1 in terms of spots, wrinkles, and pores; however, only red areas were significantly different ($p<0.001$). All side effects in the 3 groups were transient and gradually subsided after 1 to 3 months.

Conclusion: Picosecond alexandrite laser treatment using DLA showed comparable efficacy with TCC for the treatment of melasma. Improvements in texture, spots, wrinkles, and pores were observed in the laser groups. Patients with melasma lesions that exhibit telangiectasia may benefit from additional laser treatment sessions.

Introduction

Though generally regarded as a pigmentary disorder, recent evidence has demonstrated melasma to be a photoaging disorder.¹ The histological findings of melasma are similar to photoaging and include solar elastosis, increased mast cells, and sebaceous glands, as well as altered basal membranes and vascularisation.²⁻⁴ Confocal and multiphoton microscopies have also identified dermal melanophages, which are indicators of prior inflammatory response and dermal pigment presence, demonstrating that all melasma are of the mixed type.^{5, 6} The US Food and Drug Administration has approved a modified combination of the Kligman formulation, containing 4% hydroquinone, 0.05% tretinoin, and 0.01% fluocinolone acetonide, for melasma treatment. This modified combination is also known as a triple combination cream (TCC), which remains to be the gold standard treatment of melasma. The

TCC can interfere with tyrosinase activity through hydroquinone, whereas retinoic acid exerts anti-aging and peeling effects, and corticosteroid can decrease the mild inflammation associated with photodamage.

Since 2007, 1064-nm Q-switched neodymium-doped yttrium aluminium garnet (QS-Nd:YAG) laser toning has been commonly prescribed for the treatment of melasma.⁷⁻¹¹ However, in Asians, this treatment typically only produces temporary improvements along with certain side effects such as recurrence, hypopigmentation, and rebound hyperpigmentation.^{11, 12} The use of low-energy, low-density, energy-based devices such as a 1927- or 1440-nm non-ablative fractional diode laser and a 1550-nm non-ablative fractional laser have achieved variable success in darker skin types.¹³⁻¹⁵

The pathogenesis of melasma is multifactorial and complicated, and the therapeutic modality should target not only melanin but also photoaging and dermal inflammation. A novel 755-nm picosecond (ps) alexandrite laser has shown promising results in tattoo and pigmented lesions.^{16, 17} With an extremely short pulse duration of 550–750 ps, this laser produces a mainly photomechanical and less photothermal effect, which causes pigment fragmentation while simultaneously minimising collateral thermal damage and inflammation to the surrounding tissue.¹⁸ Furthermore, a diffractive lens array (DLA), which is an innovative optical attachment for the ps laser, was developed to redistribute energy into high-density pulses, similar to the concept of a fractional laser. The DLA creates laser-induced optical breakdown (LIOB),¹⁹ which is associated with dermal remodelling and deposition of new dermal collagen, elastic tissue, and mucin.²⁰

The objective of this study was to compare the effectiveness and tolerance of a ps 755-nm alexandrite laser with a DLA with those of a TCC for the treatment of melasma in female Asian patients. We hypothesised that reversal of photodamage with dermal remodelling will result in the improvement of melasma.

Materials and Methods

Type of study

This was a prospective, randomised investigator-blinded study performed in a single centre between 1 January 2017 and 31 December 2017. This study was registered with the Taiwan Ministry of Health and Welfare Clinical Trial Center (MOHW106-TDU-B-212-113004) and approved by the Institutional Review Board Ethical Committee of China Medical University Hospital (No. 105-REC1-135).

Patients

From 1 January 2017 to 31 December 2017, female patients aged 27–55 years (43.75 ± 8.15 years) who demonstrated Fitzpatrick skin type IV were consecutively enrolled in this study from a single medical centre. Patients who had received cosmetic treatment, including laser, intense pulsed light, chemical peeling, and oral tranexamic acid or bleaching agents in the year prior to enrolment were excluded. None of the patients had a history of photosensitivity or autoimmune disease. Intake of oral contraceptive pills and hormone replacement therapy were forbidden in the 6 months preceding the study and during the study period. After the evaluation, 29 eligible patients were consecutively enrolled from March 2017 to June. All the participants provided informed consent before their inclusion in the study. They were allowed to drop out anytime during the trial without any explanation to the principal investigators.

Randomisation

Randomisation was performed directly in the aesthetic medical centre of China Medical University Hospital. Twenty-nine patients were randomly assigned to 3 groups. Groups A1 and A2 received treatment with a ps alexandrite laser with a DLA at 4-week intervals. Groups A1 and A2 received 3 and 5 courses of laser treatment. The patients in group B applied topical TCC once daily (Fig. 1a).

Calculation of the sample size

The sample size population was not calculated. Patients were included consecutively during the study period.

Baseline assessments

All 3 groups were assessed considering the Melasma Area and Severity Index (MASI), an outcome measure developed by Kimbrough-Green et al,²¹ at baseline before treatment (week 0). Two blinded independent physicians (1 dermatologist and 1 plastic surgeon) calculated the MASI score in each group.

The laser groups had additional VISIA® (Canfield Scientific, Inc., NJ) complexion assessment at baseline. Standardised photographs were taken with VISIA® from the front and side of both cheeks with a standardised fluorescent light, the same background, and by the same camera with a fixed angle, flash, and distance.

Intervention

Laser

All of the patients in groups A1 and A2 had pigmented lesions, and the remainder of the whole face was treated with a ps 755-nm alexandrite laser (PicoSure®, Cynosure, MA, USA) with a DLA (FOCUS Lens Array).

The following settings were used for the 755-nm ps laser with a DLA: a fluence of 0.4 J/cm² with an 8-mm spot size and 750-ps pulse duration. Owing to the DLA, the fluence of high-energy zones (microbeams, 10% of tissue) was approximately 2.8 J/cm², and 90% of tissue (the low fluence background) received only 0.13 J/cm². This type of energy delivery is more suitable for darker skin types and melasma lesions. The 8-mm spot size has approximately 230 microbeams. The number of microbeams increases with increased spot size, but the fluence per microbeam decreases as the energy is distributed over a larger area. For this reason, we used an 8-mm instead of a 6-mm spot size. Two treatment cycles were

performed on the whole face with a total number of counts of approximately 2500. The end point of each treatment session was mild erythema.

Triple combination cream

The patients in group B were asked to apply a fixed TCC of fluocinolone acetonide 0.01% + hydroquinone 4% + tretinoin 0.05% (Tri-Luma; Galderma, Lausanne, Switzerland) on the affected facial melasma areas every night for 8 consecutive weeks. In case of skin irritation, they were allowed to alter the product application frequency after 8 weeks, that is, twice weekly in the following 6 weeks and once weekly in the final 6 weeks until the 20th week.

Post-intervention skin care

Patients were asked to apply the same baby wash (Cetaphil®, DermoPediatrics™) and moisturising lotion (Cetaphil®, DermoPediatrics™) twice daily and broad-spectrum sunscreen with a sun protection factor of 50+, PA++++ (Cetaphil®, Daylong™) every 2 hours during the daytime. Other bleaching agents such as topical kojic acid, arbutin, vitamin C, topical retinoic acid, and facial scrubs were avoided after the intervention.

Post-intervention evaluation and follow-up

All 3 groups had MASI evaluation and follow-ups at week 12 (4 weeks after the third laser session, in both laser groups) and week 20 (4 weeks after the fifth laser session in group A2 and 12 weeks after the third laser session in group A1). Two blinded independent physicians (1 dermatologist and 1 plastic surgeon) reviewed the clinical photographs before and after either laser or TCC therapy to determine the degree of clinical improvement, MASI score, and presence of any complications. Therefore, at the time of the second evaluation at week 20, group A1 had a 3-month follow-up and group A2 had a 1-month follow-up.

The 2 laser groups had additional VISIA® evaluations at weeks 12 and 20 (Fig. 1b). The VISIA® evaluation included spots, wrinkles, texture, pores, UV spots, brown spots, red areas, and porphyrins on the forehead, bilateral malar areas, and chin. The VISIA® score was presented with percentile ranking; a higher score indicates a better skin condition.

Statistical analyses

The baseline data (age and MASI score) between the 3 study groups were compared using a one-way analysis of variance (ANOVA). The MASI scores between both follow-up evaluations (weeks 12 and 20) and baseline were compared using the generalised estimating equation (GEE). The change in MASI scores from baseline to post-treatment evaluations among the 2 groups was also compared using GEE. The percentile ranking improvements in the VISIA® analysis (from baseline to week 12 or 20) were tested in the 2 laser groups using a paired sample *t*-test. The percentile ranking improvements in the VISIA analysis (from baseline to week 12 or 20) between 3 (A1) and 5 laser sessions (A2) were compared using an independent sample *t*-test. A two-sided *p* value of <0.05 was considered statistically significant, and no adjustments for multiple testing (multiplicity) was made in this study. Data analyses were conducted using SPSS version 22 (IBM Corp, Armonk, NY, USA).

Results

Patients' characteristics

The study was completed by 9, 11, and 6 patients in groups A1, A2, and B, respectively (Fig. 1a). Three (3/9, 33.33%) of the patients in group B were lost to follow-up during the study. The key characteristics of the participants at baseline are summarised in Table 1. Before treatment, the MASI scores of the groups with 3 laser sessions (A1), 5 laser sessions (A2), and topical TCC (B) were 7.8 ± 5.1 , 10.6 ± 4.4 , and 11.8 ± 5.0 , respectively. ANOVA revealed no significant difference in baseline MASI scores among the 3 groups ($p = 0.240$).

MASI evaluation of melasma improvement

The MASI scores were significantly improved in all the groups at weeks 12 and 20 (Table 2). At week 12, the MASI score in groups A1, A2, and B were 5.3 ± 3.9 , 8.2 ± 3.3 , and 7.8 ± 3.1 , respectively, all showing significant improvement, although the improvement rates in each group were not significantly different. At week 20, the MASI score in groups A1, A2, and B were 3.6 ± 2.9 , 6.6 ± 3.2 , and 5.9 ± 3.7 , respectively; all groups showed significant improvement (Fig. 2a). However, the most remarkable improvement rate (53%) was observed in group A1 (3 laser sessions), followed by groups B (topical application of TCC; 50%) and A2 (5 laser sessions; 38%). Fig. 2b demonstrates MASI changes from baseline in the 3 groups. The clinical improvement photographs after 3 and 5 laser sessions are shown in Figs. 3 and 4, respectively.

VISIA® analysis

The VISIA® imaging system analysis revealed an improvement in spots, wrinkles, texture, pores, UV spots, brown spots, and porphyrins in the 2 laser treatment groups (Fig. 5). After 3 laser sessions, significant percentile ranking improvements in spots and porphyrins ($p < 0.05$) in group A1, and in spots, pores, and brown spots ($p < 0.05$) in group A2 were observed at

week 12 (Fig. 6). While the patients in group A1 did not receive additional laser treatments, the appearance of wrinkles, texture, and pores continued to improve, while pigmented lesions such as UV and brown spots slightly regressed; however, neither showed significant differences (Supp 1). When comparing week 20 results with the baseline values, the patients who received 5 laser sessions showed greater improvements in spots, wrinkles, pores, UV spots, brown spots, and red areas, although only red areas showed significant differences ($p < 0.05$; Fig. 2b).

Side effects

Three patients in group B were lost to follow-up during the study. Of the remaining 6 patients in group B, 33.3% (2/6) reported dryness, erythema, and itching. Of the patients in group A1, who received 3 laser sessions, 22.2% (2/9) reported erythema and 11.1% (1/9) had focal desquamation. Among the patients in group A2, who received 5 laser sessions, 27.3% (3/11) reported erythema, 18.2% (2/11) had post-inflammatory hyperpigmentation (PIH), and 9.1% (1/11) had focal desquamation. All side effects gradually subsided after 1 to 3 months, and none of the patients developed hypopigmentation or further side effects. No recurrences of melasma were observed during follow-up.

Discussion

TCC is the first-line and gold standard treatment for melasma but is hardly effective in markedly photodamaged skin, as demonstrated by Raman spectroscopy by Moncada et al.²² The mean age of the participants was 43.75 ± 8.15 years, and we assumed that patients in this age group did not have severe photodamage. This could also potentially explain why our patients demonstrated good results after TCC treatment. The optimal duration of TCC treatment is daily over a period of 16 weeks. However, skin irritation often results in poor compliance in real-world practice. In our study, TCC was applied daily for 8 weeks, and in case of skin irritation, patients were allowed to taper down to twice weekly in the following 6 weeks and once weekly in the final 6 weeks until the final evaluation at week 20. The relatively short duration of TCC cream use was a limitation in our study. However, even with this relatively short duration, TCC was already as effective as the ps alexandrite laser treatment with DLA for melasma. In a study performed by Torok et al., among 569 patients, 327 completed 12 months of treatment and 80% had lesions, which nearly all cleared up by month 12.²³ It could be assumed that continuing the TCC use for a further 16 weeks would lead to significantly better results than laser treatment.

With regards to the side effects, 25% (5/20) of the patients in the laser treatment groups reported erythema and 33.3% (2/6) in the TCC group reported dryness, erythema, and itching. PIH occurred in 18.2% (2/11) of patients who had 5 laser treatment sessions. All of the above-mentioned side effects gradually subsided after 1 to 3 months since the intervention. During the limited follow-up period of 3 months for group A1 (3 laser sessions) and the TCC group, and 1 month for group A2, no recurrences were observed. In our study, the safety profile of the TCC and ps 755-nm alexandrite laser with a DLA were similar. However, longer follow-up periods are needed because melasma tends to recur.

In this study, we found that patients who received 3 laser sessions showed a greater MASI improvement rate (53%) than those who received 5 laser sessions (38%), although the difference did not reach statistical significance. These findings may be due to the fact that at week 20, the patients who received 3 laser sessions had a longer period (12 weeks) to reduce inflammation triggered by the laser treatment than those who received 5 laser sessions (4 weeks). Therefore, time intervals should be no <4 weeks to allow for healing from inflammation. The laser energy we used in this study was low. The average fluence of the entire treated area was 0.4 J/cm². However, temporary PIH remained in 18.2% (2/11) of the patients who had 5 laser sessions. Therefore, laser intervals longer than 4 weeks, with even lower energy, may be safer for Asian patients with melasma.

Wrinkles and pigmentary changes are major features of photoaging in Asians.²⁴ The 755-nm ps laser with DLA serves as a safe and effective non-ablative modality for darker individuals for improving skin texture, photoaging, skin tightening, and non-ablative rejuvenation.^{20, 25-27} LIOB was more prominent in darker skin types owing to the increased melanin in the granular layer of the epidermis.^{19, 28} In our study, in addition to improvements in melasma and spots, wrinkles, texture, pores, and red areas after laser sessions, 5 laser sessions offered a greater overall improvement in comparison with only 3 laser sessions. These findings suggest that photoaging may be reversed by neocollagenesis triggered by LIOB. The mean age of our participants was 43.75 ± 8.15 years. Older patients with melasma and more extensive photodamage are expected to respond better to laser treatment. In group A1, even after laser treatment had been stopped for 12 weeks, the skin texture, pores, and wrinkles continued to improve. We hypothesised that this is due to the continuous neocollagenesis from the last laser session.

In the present study, the red areas significantly improved after 5 laser sessions as compared with the results of only 3 laser sessions. However, 5 laser sessions did not lead to more significant improvements of melasma lesions. Fractional ps laser may play a role in

normalising the vasculature; however, the significance of the increased vascularisation in melasma remains poorly understood. Photoaged skin has been reported to display an age-dependent reduction of cutaneous microvasculature,² whereas increased vascularity is a major finding in melasma.⁴ VEGF expression level was significantly increased in melasma⁴ and significantly reduced after treatment with pulsed dye laser and intense pulsed light.²⁹ Moreover, Regazzetti et al. proved that endothelin, released by microvascular endothelial cells, can induce melanogenesis,³⁰ with its levels significantly decreasing after oral tranexamic acid treatment.³¹ The efficacy of 755-nm ps laser with DLA in melasma lesions, which had a vascular component, needs to be confirmed in a larger population.

This study has a few limitations. First, the study sample size was small, and all of the patients were Asian females from a single tertiary referral centre. Second, we did not perform skin biopsies and additional histological studies, which are required to confirm that a ps 755-nm alexandrite laser with a DLA can reverse photoaging. Third, the follow-up period in this study was 3 months in groups A1 and B and only of 1 month in group A2. A longer follow-up period is required to address the recurrence of melasma. Finally, not all the patients in group B used TCC daily until the 20th week of evaluation.

Conclusion

Our study used VISIA® analysis to show that signs of photoaging could be reversible by a ps 755-nm alexandrite laser with a DLA. Picosecond alexandrite lasers with a DLA showed comparable efficacy as TCC topical therapy for the treatment of melasma in female Asian patients. Patients with melasma lesions exhibiting telangiectasia may benefit from more laser sessions. However, laser treatment intervals of >4 weeks with low fluence may be safer. Ps 755-nm laser with a DLA is an interesting option to be considered for treating melasma. This still needs to be confirmed in a larger population, with a longer follow-up and duration of TCC use.

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Conflict of Interests: None declared.

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References

- 1 Passeron T, Picardo M. Melasma, a photoaging disorder. *Pigment cell & melanoma research*. 2018;31; 461-465.
- 2 Chung JH, Eun HC. Angiogenesis in skin aging and photoaging. *The Journal of dermatology*. 2007;34; 593-600.
- 3 Handa S, De D, Khullar G, Radotra BD, Sachdeva N. The clinicoaetiological, hormonal and histopathological characteristics of melasma in men. *Clinical and experimental dermatology*. 2018;43; 36-41.
- 4 Kim EH, Kim YC, Lee ES, Kang HY. The vascular characteristics of melasma. *Journal of dermatological science*. 2007;46; 111-116.
- 5 Kang HY, Bahadoran P, Suzuki I, Zugaj D, Khemis A, Passeron T, et al. In vivo reflectance confocal microscopy detects pigmentary changes in melasma at a cellular level resolution. *Experimental dermatology*. 2010;19; e228-233.
- 6 Lentsch G, Balu M, Williams J, Lee S, Harris RM, Konig K, et al. In vivo multiphoton microscopy of melasma. *Pigment cell & melanoma research*. 2019;32; 403-411.
- 7 Kaminaka C, Furukawa F, Yamamoto Y. The Clinical and Histological Effect of a Low-Fluence Q-Switched 1,064-nm Neodymium: Yttrium-Aluminum-Garnet Laser for the Treatment of Melasma and Solar Lentigenes in Asians: Prospective, Randomized, and Split-Face Comparative Study. *Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al]*. 2017;43; 1120-1133.
- 8 Fabi SG, Friedmann DP, Niwa Massaki AB, Goldman MP. A randomized, split-face clinical

trial of low-fluence Q-switched neodymium-doped yttrium aluminum garnet (1,064 nm) laser versus low-fluence Q-switched alexandrite laser (755 nm) for the treatment of facial melasma. *Lasers in surgery and medicine*. 2014;46; 531-537.

9 Lee MC, Chang CS, Huang YL, Chang SL, Chang CH, Lin YF, et al. Treatment of melasma with mixed parameters of 1,064-nm Q-switched Nd:YAG laser toning and an enhanced effect of ultrasonic application of vitamin C: a split-face study. *Lasers in medical science*. 2015;30; 159-163.

10 Chen YT, Chang CC, Hsu CR, Shen JH, Shih CJ, Lin BS. Combined vitamin C sonophoresis and neodymium-doped yttrium aluminum garnet (NdYAG) laser for facial hyperpigmentation: An outcome observation study in Asian patients. *Indian journal of dermatology, venereology and leprology*. 2016;82; 587.

11 Wattanakrai P, Mornchan R, Eimpunth S. Low-fluence Q-switched neodymium-doped yttrium aluminum garnet (1,064 nm) laser for the treatment of facial melasma in Asians. *Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al]*. 2010;36; 76-87.

12 Wang YJ, Chang CC. Epidermal grafting for leukoderma resulting from 1064-nm quality-switched neodymium-doped yttrium aluminium garnet laser toning. *International wound journal*. 2018.

13 Mpofana N, Abrahamse H. The Management of Melasma on Skin Types V and VI Using Light Emitting Diode Treatment. *Photomedicine and laser surgery*. 2018;36; 522-529.

14 Vanaman Wilson MJ, Jones IT, Bolton J, Larsen L, Fabi SG. The Safety and Efficacy of Treatment With a 1,927-nm Diode Laser With and Without Topical Hydroquinone for Facial Hyperpigmentation and Melasma in Darker Skin Types. *Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al]*. 2018;44; 1304-1310.

15 Kroon MW, Wind BS, Beek JF, van der Veen JP, Nieuweboer-Krobotova L, Bos JD, et al. Nonablative 1550-nm fractional laser therapy versus triple topical therapy for the treatment of melasma: a randomized controlled pilot study. *Journal of the American Academy of Dermatology*. 2011;64; 516-523.

16 Lorgeou A, Perrillat Y, Gral N, Lagrange S, Lacour JP, Passeron T. Comparison of two picosecond lasers to a nanosecond laser for treating tattoos: a prospective randomized study on 49 patients. *Journal of the European Academy of Dermatology and Venereology : JEADV*. 2018;32; 265-270.

17 Levin MK, Ng E, Bae YS, Brauer JA, Geronemus RG. Treatment of pigmentary disorders in patients with skin of color with a novel 755 nm picosecond, Q-switched ruby, and Q-switched Nd:YAG nanosecond lasers: A retrospective photographic review. *Lasers in surgery and medicine*. 2016;48; 181-187.

18 Freedman JR, Kaufman J, Metelitsa AI, Green JB. Picosecond lasers: the next generation of short-pulsed lasers. *Seminars in cutaneous medicine and surgery*. 2014;33; 164-168.

- 19 Tanghetti EA. The histology of skin treated with a picosecond alexandrite laser and a fractional lens array. *Lasers in surgery and medicine*. 2016;48; 646-652.
- 20 Wat H, Yee-Nam Shek S, Yeung CK, Chan HH. Efficacy and safety of picosecond 755-nm alexandrite laser with diffractive lens array for non-ablative rejuvenation in Chinese skin. *Lasers in surgery and medicine*. 2018.
- 21 Kimbrough-Green CK, Griffiths CE, Finkel LJ, Hamilton TA, Bulengo-Ransby SM, Ellis CN, et al. Topical retinoic acid (tretinoin) for melasma in black patients. A vehicle-controlled clinical trial. *Archives of dermatology*. 1994;130; 727-733.
- 22 Moncada B, Castillo-Martinez C, Arenas E, Leon-Bejarano F, Ramirez-Elias MG, Gonzalez FJ. Raman spectroscopy analysis of the skin of patients with melasma before standard treatment with topical corticosteroids, retinoic acid, and hydroquinone mixture. *Skin research and technology : official journal of International Society for Bioengineering and the Skin (ISBS) [and] International Society for Digital Imaging of Skin (ISDIS) [and] International Society for Skin Imaging (ISSI)*. 2016;22; 170-173.
- 23 Torok H, Taylor S, Baumann L, Jones T, Wieder J, Lowe N, et al. A large 12-month extension study of an 8-week trial to evaluate the safety and efficacy of triple combination (TC) cream in melasma patients previously treated with TC cream or one of its dyads. *Journal of drugs in dermatology : JDD*. 2005;4; 592-597.
- 24 Chung JH, Lee SH, Youn CS, Park BJ, Kim KH, Park KC, et al. Cutaneous photodamage in Koreans: influence of sex, sun exposure, smoking, and skin color. *Archives of dermatology*. 2001;137; 1043-1051.
- 25 Brauer JA, Kazlouskaya V, Alabdulrazzaq H, Bae YS, Bernstein LJ, Anolik R, et al. Use of a picosecond pulse duration laser with specialized optic for treatment of facial acne scarring. *JAMA dermatology*. 2015;151; 278-284.
- 26 Huang CH, Chern E, Peng JH, Hsien-Li Peng P. Noninvasive Atrophic Acne Scar Treatment in Asians With a 755-nm Picosecond Laser Using A Diffractive Optic Lens-A Retrospective Photographic Review. *Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al]*. 2018.
- 27 Haimovic A, Brauer JA, Cindy Bae YS, Geronemus RG. Safety of a picosecond laser with diffractive lens array (DLA) in the treatment of Fitzpatrick skin types IV to VI: A retrospective review. *Journal of the American Academy of Dermatology*. 2016;74; 931-936.
- 28 Tanghetti Md E, Jennings J. A comparative study with a 755 nm picosecond Alexandrite laser with a diffractive lens array and a 532 nm/1064 nm Nd:YAG with a holographic optic. *Lasers in surgery and medicine*. 2018;50; 37-44.
- 29 Hassan AM, Elfar NN, Rizk OM, Eissa NY. Pulsed dye laser versus intense pulsed light in melasma: a split-face comparative study. *The Journal of dermatological treatment*. 2018;29; 725-732.
- 30 Regazzetti C, De Donatis GM, Ghorbel HH, Cardot-Leccia N, Ambrosetti D, Bahadoran P,

et al. Endothelial Cells Promote Pigmentation through Endothelin Receptor B Activation. The Journal of investigative dermatology. 2015;135; 3096-3104.

31 Kim SJ, Park JY, Shibata T, Fujiwara R, Kang HY. Efficacy and possible mechanisms of topical tranexamic acid in melasma. Clinical and experimental dermatology. 2016;41; 480-485.

Figure legends

Figure 1 (a) Study design (b) Both laser groups had laser sessions every 4 weeks and Melasma Area and Severity Index (MASI) score and VISIA® evaluations at baseline week 12 and week 20.

Figure 2

(a) Melasma Area and Severity Index (MASI) scores at baseline, week 12, and week 20 in each study group. The values statistically significantly differed among the time points in each study group.

****p < 0.01, ***p < 0.001.**

Group A received treatment with a ps alexandrite laser with a diffractive lens array in 4-week intervals; group A1, 3 courses of laser treatment; and group A2, 5 courses of laser treatment. The patients in group B applied topical TCC once daily for at least 8 weeks.

(b) Change in MASI score from baseline in the 3 groups.

Figure 3

Melasma in a 40 year old woman. Front view (a) Baseline MASI score, 4.7 (b) After 3 sessions of ps 755 nm alexandrite laser with diffractive arrays. MASI score, 3.0 (c) Three month follow-up after the third laser session. MASI score, 2.4

Figure 4

Melasma in a 48 year old woman (a, d) Baseline. MASI score, 2.4 (b, e), after 3 sessions of ps 755 nm alexandrite laser with diffractive arrays. MASI score, 1.8, (c, f) after 5 laser sessions. MASI score, 1.8.

Figure 5

Improvements of both melasma lesions and signs of photoaging, including wrinkles, texture, and pores, after ps 755-nm alexandrite laser with a diffractive array. (a) Baseline, (b) after 3 laser sessions, and (c) after 5 laser sessions.

Figure 6

Comparisons of VISIA® percentile ranking between after laser sessions and baseline in 2 laser treatment groups

(a) General Light: spots, wrinkles, texture, and pores at baseline, week 12, and week 20 in groups A1 and A2.

(b) Cross-polarised/UV Light: UV spots, brown spots, red areas, and porphyrins at baseline, week 12, and week 20 in groups A1 and A2.

Group A1: 3 laser sessions. Group A2: 5 laser sessions.

PR: percentile ranking

Data are presented as mean \pm standard error (SE).

Comparisons of VISIA® percentile ranking between baseline and post-intervention are analysed on the basis of p values. *p < 0.05.

Table 1. Key Characteristics of the Participants at Baseline

Characteristic	Group A1 (n=9)	Group A2 (n=11)	Group B (n=6)
Age			
Mean (yr)	40.4	46.4	50.0
<40 yr	3	1	0
40–54 yr	6	9	6
≥55 yr	0	1	0
MASI score†	7.8±5.1	10.6±4.4	11.8±5.0

Data are given as mean ± standard deviation.

MASI score†: Melasma Area and Severity Index score.

Group A1 received three sessions of laser treatment. Group A2 received five sessions of laser treatment. Group B received triple combination cream therapy.

Table 2. Post-Intervention MASI Scores (Mean \pm Standard Deviation) of All Participants

	Group A1	Group A2	Group B
MASI [†] score			
Baseline	7.8 \pm 5.1	10.6 \pm 4.4	11.8 \pm 5.0
Week 12	5.3 \pm 3.9**	8.2 \pm 3.3**	7.8 \pm 3.1**
Week 20	3.6 \pm 2.9**	6.6 \pm 3.2***	5.9 \pm 3.7***
MASI score [†]			
Change (week 12 - baseline)	-2.50	-2.46	-4.07
Change (week 20 - baseline)	-4.13	-4.02	-5.95

Data are given as mean \pm standard deviation.

MASI score[†]: Melasma Area and Severity Index score.

Comparisons of MASI score between post-intervention and baseline were analysed and P-values were generated. ** indicates P-value < 0.01. *** indicates P-value < 0.001.











