

Split-Face Study Using a 1,927-nm Thulium Fiber Fractional Laser to Treat Photoaging and Melasma in Asian Skin

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BACKGROUND Although the 1,927-nm thulium fiber fractional laser is effective and safe for treating photoaging, clinical data regarding this modality remain limited.

OBJECTIVE To investigate the efficacy and safety of the 1,927-nm thulium fiber fractional laser for treating photoaging and melasma in Asians.

METHODS Twenty-five participants received three laser treatments (at 3-week intervals) on the half of the face with more-severe photoaging and melasma. Independent investigators evaluated clinical improvement 2 and 6 months after the final treatment. Improvement in melasma was evaluated using the Melasma Area and Severity Index. Subjective satisfaction rates were also evaluated. Adverse events were assessed, and pain was scored using a visual analog scale (VAS). Histologic changes were observed using immunohistochemical staining.

RESULTS Clinical improvement of photodamaged facial skin was remarkable on the treatment side. Most participants reported that their subjective satisfaction rate was greater than slight satisfaction. Downtime for healing required approximately 1 week. No severe adverse events occurred. Mean VAS score during treatment was 4.8. Collagen regeneration and melanin decrease were observed histologically.

CONCLUSION The 1,927-nm thulium fiber fractional laser is a safe, effective treatment for photoaging and melasma in Asians.

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The demand for safe and effective treatment of photoaging has risen steadily over the last several decades with an aging demographic shift of our population. The standard for photorejuvenation has been ablative resurfacing with carbon dioxide (CO₂, 10,600 nm) or erbium-doped yttrium aluminum garnet (Er:YAG, 2,940-nm) lasers.¹ Such complete epidermal ablation has greater risk of infection, scarring, and postinflammatory hyperpigmentation (PIH). Fractional photothermolysis (FP) has been introduced as a way to overcome the limitations of traditional ablative resurfacing. FP is a new technique for the treatment

of skin lesions in which an array of microscopic thermal wounds (microscopic treatment zones) is induced in the skin to stimulate a therapeutic response deep in the dermis. This new modality of laser skin resurfacing was developed to provide a successful clinical response comparable with that of traditional ablative resurfacing but with shorter recovery time and fewer complications, but FP may result in PIH, which is more common in Asians.² In addition, several recent reports suggest that fractional laser treatment is not effective in treating pigmentary lesions such as melasma,^{3,4} whereas a group of U.S. researchers recommends the

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fractional laser as the first choice of laser therapy for melasma.⁵

Characteristic features of photodamage well-documented in Asian skin include discrete pigmentary change.⁶ The majority of the Asian population has darker skin, usually Fitzpatrick skin types III and IV, than Caucasians. The higher melanin content appears to make Asian skin more susceptible to pigmentary change than to skin wrinkling as a result of photoaging.⁷ Therefore, the treatment modality that optimally reduces the risk of PIH while effectively treating the pigmentary changes is ideal for photoaging therapy in Asians.

A new addition to the 1,550-nm erbium:glass (Er:glass) fractional device using the novel 1,927-nm wavelength (Fraxel re:store DUAL, Solta Medical, Hayward, CA) was introduced in October 2009. This wavelength has a higher absorption coefficient for water than the fractional 1,550-nm Er:glass fractional laser, making it possible to target epidermal processes such as pigmentation and dyschromia. The other characteristic of the 1,927-nm wavelength that makes it well-suited for superficial epidermal indications is its 200- μm maximum penetration depth, compared with 1,400 to 1,500 μm for the 1,550-nm wavelength. Although it was reported that the 1,927-nm thulium fiber fractional laser for nonfacial photo-damaged skin and melasma is effective and safe,^{8,9} clinical data regarding this modality are limited.

The aim of this study was to investigate the efficacy and safety of 1,927-nm thulium fiber fractional laser resurfacing to improve photoaging and melasma in Asian facial skin. To our knowledge, this is the first split-face study using this novel laser.

Subjects and Methods

Participants

We performed a prospective, split-face, single-blinded study to investigate the efficacy and safety of 1,927-nm thulium fiber fractional laser resurfacing

to improve photoaging and melasma in Asian skin. Twenty-five participants (all female) with photoaged facial skin were included. Eight had melasma that a dermatologist had diagnosed. Participants' ages ranged from 30 to 60 (mean 43.1 ± 10.4), and they had Fitzpatrick skin types III ($n = 23$) and IV ($n = 2$). Informed consent was obtained from all enrolled patients, and the Institutional Review Board of the Asan Medical Center, Seoul, Korea, approved the study, which was conducted in accordance with the 1975 Declaration of Helsinki concerning use of human subjects. Patients were excluded from the study if they had active infections, current pregnancy, a history of isotretinoin use in the year before laser treatment, a history of keloid scarring, or a known allergy to topical lidocaine anesthetic; had undergone the use of a topical bleaching agent, such as hydroquinone, within 2 months; or had had any cosmetic procedure performed in the treatment areas within 6 months before enrollment.

Treatments

We used a novel 1,927-nm thulium fiber fractional laser (Fraxel re:store DUAL). In each patient, the appropriate skin area was cleansed before treatment using a mild cleanser. A topical anesthetic cream (Emla, AstraZeneca, Wilmington, DE) was applied to the treatment area for 1 hour under occlusion before laser treatment. Participants underwent three treatment sessions at 3-week intervals. Patients received laser treatment on the half of the face that contained more-severe photoaging and melasma (treatment side). No laser treatment was performed on the other half of the face (control side). Treatments were performed at an energy of 10 mJ. Ten passes at the aforementioned settings were performed at each treatment at level 3 (30% surface area coverage). A cooling device (Zimmer Elektromedizin Cryo 5 device, Zimmer Medizin Systems, Irvine, CA) was used to mitigate participant discomfort (fan power 5–7; integrated into hand piece). Participants were advised to avoid sun exposure after the laser treatment and to use daily

broad-spectrum sunscreen. Participants were also advised not to use any bleaching agent during the treatment and follow-up periods.

Clinical Evaluation

Follow-up was at 2 and 6 months after the final treatment session. Standardized digital photographs were taken (Nikon D30, Nikon Corporation, Tokyo, Japan) at baseline and follow-up. Two independent investigators evaluated the photographs for clinical improvement of pigmentation, wrinkles, laxity, and overall features of both facial sides (treatment side and control side) on a 6-point scale (0 = worsening; 1 = 0%, no improvement; 2 = 1–10% improvement; 3 = 11–25% improvement; 4 = 26–50% improvement; 5 = 51–75% improvement; and 6 = 76–100% improvement. We compared clinical improvement of the control and treatment sides between baseline and 2 months after the final session and between 2 and 6 months after the final treatment session.

The Melasma Area and Severity Index (MASI) was used for clinical assessment to investigate the efficacy in the treatment of melasma.¹⁰ To compare both sides of the face, we separately evaluated the MASI on the right and left sides, according to the measurements used in a previous study.¹¹

Participants provided subjective satisfaction rates of appearance of the treated versus the control facial side using a 6-level rating scale (unsatisfactory = 0%, no improvement or worsened appearance; minimal satisfaction = 1–10% improvement; mild satisfaction = 11–25% improvement; moderate satisfaction = 26–50% improvement; good satisfaction = 51–75% improvement; and excellent satisfaction = 76–100% improvement).

Throughout the study, participants were asked to report any adverse symptoms (e.g., erythema, edema, pain, crusting, infection, pigmentary change, scarring). Participants were asked to score pain

immediately after treatment based on a visual analogue scale (VAS) of 0 (no pain) to 10 (worst pain imaginable). If the participant had previously received nonablative 1,550-nm Er:glass fractional laser treatment, they were also asked to score the pain experienced during the previous treatment.

Skin Biopsy

To investigate the histologic effects of the 1,927-nm thulium fractional laser on facial skin, we took biopsy specimens at baseline and 2 months after the last treatment from two participant volunteers after obtaining written informed consent.

Skin biopsy samples were taken from patients' cheeks on the treatment side. Three- μ m-thick sections were stained with hematoxylin and eosin (H&E) and Fontana-Masson and immunostained with antibodies against melan-A (DAKO A/S, Glostrup, Denmark) and procollagen type-3 (Santa Cruz Biotechnology, Inc., Santa Cruz, CA).

Statistical Analysis

Clinical data were compared using the Wilcoxon signed rank test. We used a linear mixed model to compare the treatment effects on the MASI over time. All statistical analyses were performed using SPSS version 18.0 (SPSS, Inc., Chicago, IL), with a difference considered statistically significant when $p < .05$.

Results

All participants completed the three treatment sessions and the 2-month follow-up. After the 2-month follow-up, 18 participants were lost to follow-up because they did not want to visit our clinic. Seven participants, six of whom concurrently had melasma, were followed for 6 months after their last treatment.

Efficacy

We assessed the efficacy of 1,927-nm thulium fiber fractional laser treatment using standardized

photographs 2 and 6 months after the last treatment session. Clinical photographs demonstrating improvement of photoaged facial skin are seen in Figures 1 and 2.

Two months after the final treatment session, we assessed wrinkles, laxity, pigmentation, and overall facial features (Figure 3A). For wrinkles on the treatment side, eight participants (32%) showed greater than 50% improvement, 13 (52%) showed 11% to 50% improvement, and four (16%) showed 10% or less improvement. Regarding laxity on the treatment side, seven participants (28%) showed greater than 50% improvement, 17 (68%) showed 11% to 50% improvement, and only one (4%) showed 10% or less improvement. Regarding pigmentation on the treatment side, four participants

(16%) showed greater than 50% improvement, 14 (56%) showed 11% to 50% improvement, and seven (12%) showed 10% or less improvement. Assessing overall features, seven participants (28%) showed greater than 50% improvement, 16 (64%) showed 11% to 50% improvement, and two participants (8%) showed 10% or less improvement. On the untreated side, most participants showed 10% or less or no improvement in all of the categories. Only one participant showed 11% to 25% improvement on the untreated side. Treatment sides had statistically significantly greater improvements than control sides ($p < .001$).

Six months after the final treatment session, there was a slight decline in improvements (Figure 3B). Regarding wrinkles, four participants (57.1%)

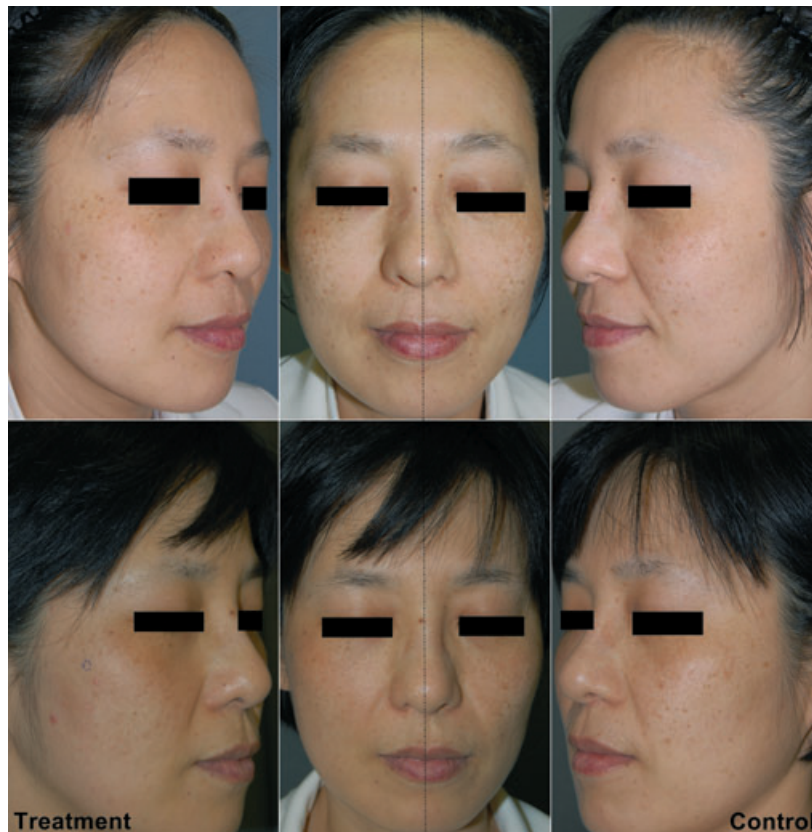


Figure 1. Photographs of a patient at baseline (upper row) and 2 months after three laser treatment sessions (lower row). Clinical improvement on the right side (treatment side) of her face were graded as 2 in wrinkles, 4 in laxity, 5 in pigmentation, and 4 in overall features; there was moderate improvement in facial photoaging. On the left side (control side), the patient showed no clinical differences between observation time points. (6-point scale: 0 = worsening; 1 = 0%, no improvement; 2 = 1–10% improvement; 3 = 11–25% improvement; 4 = 26–50% improvement; 5 = 51–75% improvement; 6 = 76–100% improvement).



Figure 2. Photographs of a patient with melasma at baseline and 2 and 6 months after three laser treatment sessions. Melasma Area and Severity Index scores were 6, 3.6, and 4.5 at each of the time points; melasma was improved after her treatment and recurred only slightly.

showed 11% to 50% improvement and three (42.9%) showed 10% or less improvement. Regarding laxity, five participants (71.5%) showed 11% to 50% improvement and two (28.5%) showed 10% or less improvement. Regarding pigmentation, four participants (57.1%) showed 11% to 50% improvement, and three (42.9%) showed 10% or less improvement. Assessing overall features, six participants (85.7%) showed 11% to 50% improvement, and one (14.3%) showed 10% or less improvement. No statistically significant differences were seen in improvements in laxity and overall appearance between 2 and 6 months after the final treatment session ($p > .05$).

MASI score

We evaluated change in mean MASI scores of six participants who had melasma and who completed the 6-month follow-up. Figure 4 shows the mean MASI score of each facial side over time. At baseline, the mean MASI score of the treatment side was significantly higher than that of the control side because we had chosen the more-severely affected side as the treatment side at baseline. On the treatment sides, mean MASI scores had decreased from 6.06 ± 0.89 to 4.04 ± 1.20 (33%) at 2-month follow-up. Mean MASI scores decreased from 6.06 ± 0.89 to 4.34 ± 1.20 (28%) between baseline and 6-month follow-up ($p < .05$) but increased slightly from 4.04 ± 1.20 to 4.34 ± 1.20

(5%) between the 2- and 6-month follow-up examinations, although the difference between mean MASI scores at 2 and 6 months was not statistically significant ($p > .05$). On the control sides, mean MASI scores decreased 5% (2 months) and 12% (6 months).

Subjective Satisfaction

All participants reported that their subjective satisfaction rate was greater than minimal satisfaction. Two and 6 months after the final laser treatment session, 80.0% and 57.1% of participants, respectively, reported their subjective satisfaction rates to be greater than moderate satisfaction (Figure 5).

Safety

In all participants, initial reactions to laser treatment consisted of erythema, edema, and microcrust formation in the treated areas. In most patients, erythema and edema subsided within 2 days. Only one participant reported prolonged erythema lasting for 4 weeks, which was mild. All participants had microcrust formation that gradually disappeared within 1 week. One participant reported severe itching, erythema, and edema. She had a past medical history of dermatographic urticaria. We speculated that these adverse events of laser treatment were associated with her dermatographic urticaria. Three participants had PIH that

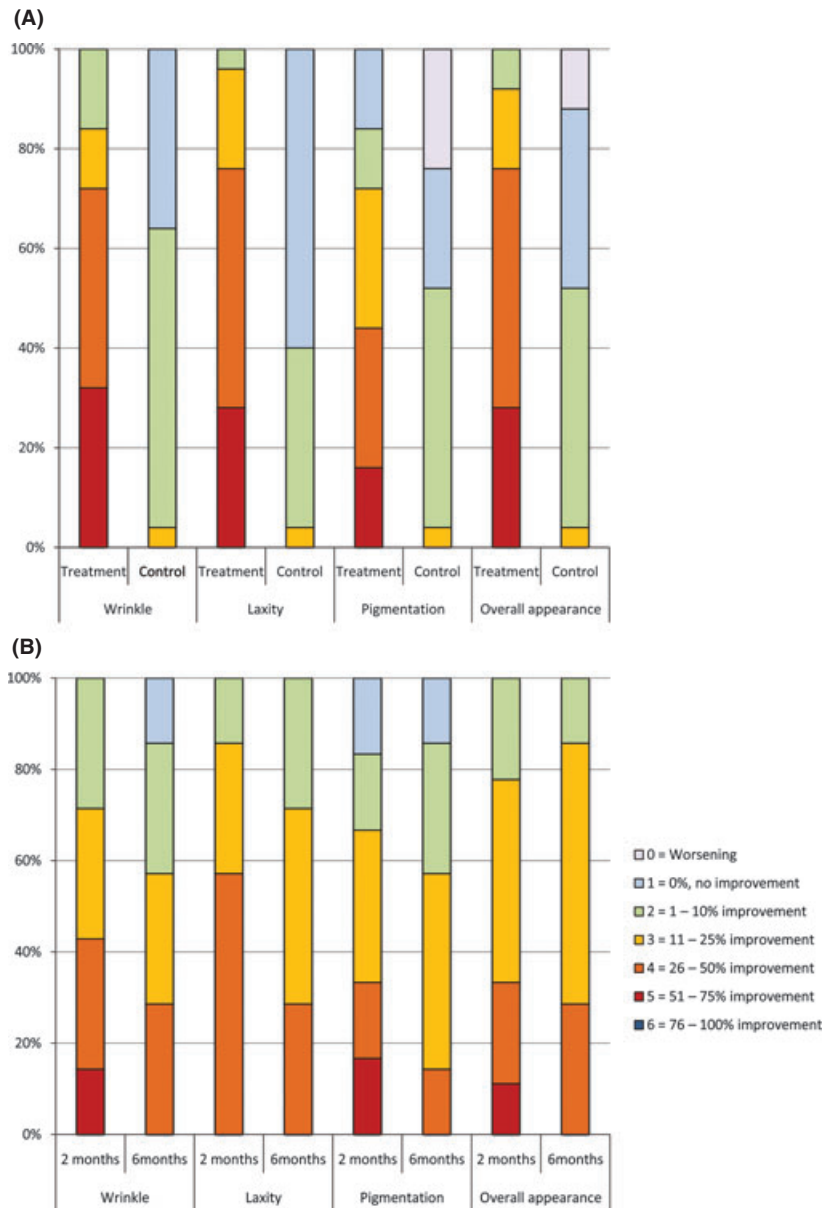


Figure 3. Clinical improvement based on standardized photographs. (A) Clinical improvement on both sides of the face (treatment and control sides) 2 months after the final laser treatment session. (B) Clinical improvement 2 and 6 months after the final treatment session.

spontaneously resolved within 3 weeks. Infection, scarring, and hypopigmentation did not occur in any patient after the treatment. No participant was lost to follow-up because of adverse events.

Seven participants indicated that they had previously undergone nonablative 1,550-nm Er:glass fractional

laser treatment. Their VAS score was recorded during both laser treatments. Mean VAS score during the laser treatment was 4.8 with the 1,927-nm thulium fiber fractional laser, which was much more tolerable than the nonablative 1,550-nm Er:glass fractional laser (mean VAS score 9.1, Figure 6).

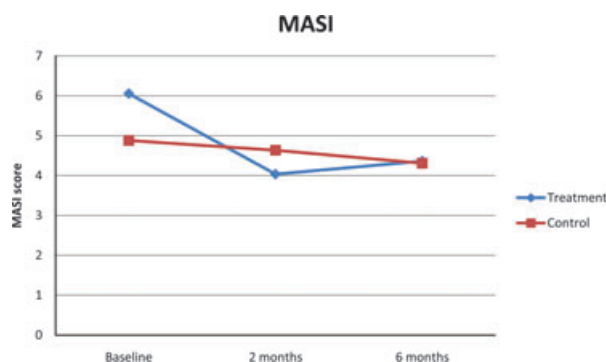


Figure 4. Changes in mean Melasma Area and Severity Index score.

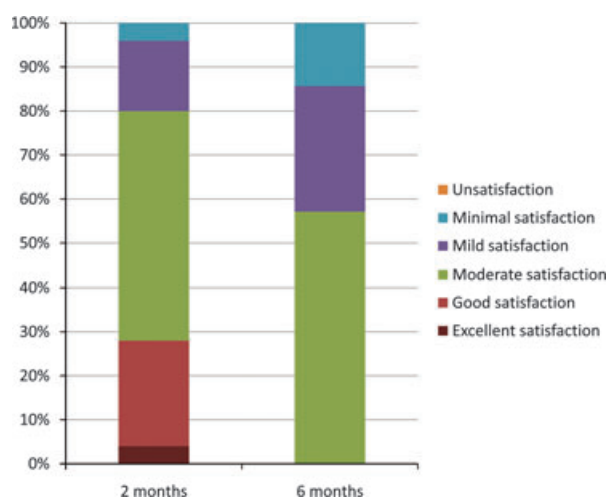


Figure 5. Subjective patient satisfaction rates 2 and 6 months after final laser treatment session. Values are cited as percentage of the total patient population (100%).

Skin Biopsy

Skin biopsies were performed in two participants at baseline and 2 months after the final treatment session. We compared the histologic changes between baseline and 2-month follow-up (Figure 7). Although H&E staining showed slight collagen regeneration, the concurrent increase in observed procollagen 3 immunostaining was marked. Melanin decrease along the basal layer was observed using Fontana-Masson staining. Melan-A immunostaining revealed no significant change in numbers of melanocytes in treated skin sections.

Discussion

Several studies support FP treatment as an effective and safe treatment of photoaged facial skin.^{12–14} Manstein and colleagues reported significant improvements in periorbital rhytides and skin texture after initial treatments with their prototype FP device.¹² Geronemus and colleagues reported improvement in fine to moderate rhytides with FP, with less efficacy for deeper wrinkle lines.¹³ Wanner and colleagues reported the nonablative 1,550-nm FP laser is an effective treatment for facial and non-facial photodamage, rhytides, and dyspigmentation with a favorable recovery and side effect profile.¹⁴

One of the novel effects of FP has been the observation of normalization of pigmentary variance after FP treatment. Previous research showed a localized, well-controlled melanin release and transport mechanism using microscopic epidermal necrotic debris (MEND) as the vehicle for pigment redistribution.^{6,12} More-recent investigations regarding this aspect of FP have led to novel concepts for treatment of dermatologic conditions characterized by pigment abnormalities, such as melasma,^{15–17} nevus of Ota,¹⁸ and minocycline-induced hyperpigmentation,¹⁹ but results of FP treatments for melasma are conflicting. Lee and colleagues suggested the judicious use of FP for melasma treatment in Asian skin because of its limited efficacy.²⁰ Wind and colleagues reported that the nonablative 1,550-nm fractional laser is not recommended in melasma treatment because of a high risk of PIH.³ Karsai and colleagues also suggested that nonablative FP did not provide a substantial benefit in treating melasma over the lone application of a broad-spectrum sunscreen.⁴

The novel 1,927-nm thulium fractional laser was introduced in October 2009. It has 10 times greater absorption coefficient for water than the 1,550-nm Er:glass fractional laser and can achieve greater surface area coverage per treatment.⁸ At maximum settings, the 1,927-nm thulium fiber laser can attain

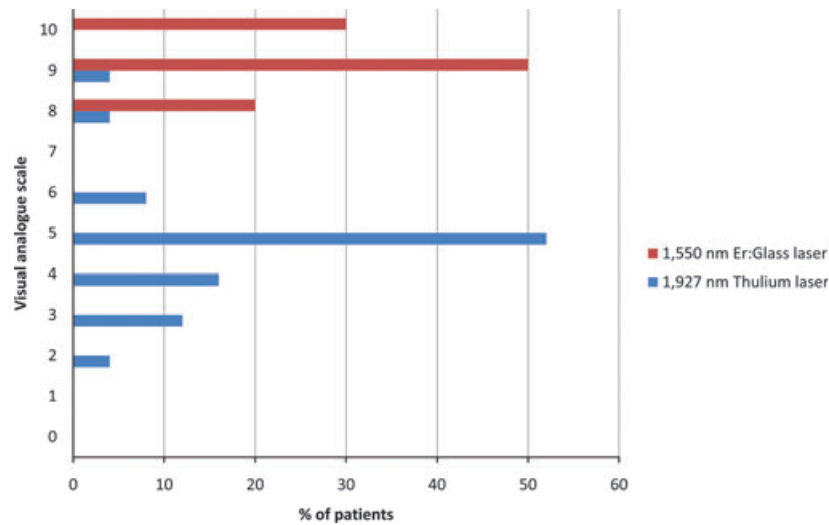


Figure 6. Analysis of pain during the laser procedures. Mean visual analog scale (VAS) score using the 1,927-nm thulium fractional laser treatment was 4.8, which was markedly lower than mean VAS score of 9.1 that resulted from using the 1,550 nm erbium:glass fractional laser treatment.

up to 70% surface area coverage per treatment. The mechanism by which lentiginos and dyspigmentation are improved using FP is through the shuttling of melanin in columns of MEND that photothermolysis creates.²¹ The extraneous pigment is then exfoliated.^{12,21} Only limited data exist regarding the efficacy and safety of the novel 1,927-nm thulium fiber fractional laser. In 2010, Polder and colleagues first reported that it was safe and effective for treatment of nonfacial photodamage.⁹ Their study, which included 1-month follow-up data from 12 nonfacial treatment sites, demonstrated photodamage and lentigine improvement at 1-month follow-up after a series of three laser treatments. Treatment areas represented in their study were the dorsal hands, bilateral circumferential forearms, neck, and chest. There was no evidence of scarring, erosions, or postinflammatory hyper- or hypopigmentation throughout the course of the study. Recently, Polder and colleagues also reported that the 1,927-nm fractional thulium fiber laser was a safe and effective treatment for melasma.⁸ A statistically significant 51% reduction in MASI score was observed 1 month after three to four laser treatments. A 33% and 34% reduction in MASI score was observed at the 3- and 6-month follow-up visits, respectively. Six

months after the final laser treatment, melasma disease severity increased marginally, although patients were still improved from baseline. Polder and colleagues explained that this most likely reflects a slight melasma recurrence that patients should be informed of before laser treatment.

Our study demonstrated that the 1,927-nm thulium fiber fractional laser was clinically and histologically effective for the treatment of photoaged facial skin, including melasma, in middle-age Asian women. Two and 6 months after three treatment sessions, participants showed clinical improvement in facial skin wrinkles, laxity, and pigmentation, although these improvements subsequently decline slightly. MASI score showed improvement of melasma 2 months after the final treatment. Our results were similar with those from Polder's study.^{8,9} We thought that the peak of clinical improvements might be between 2 and 3 months after treatments. We demonstrated that histologic changes in facial skin after 1,927-nm fractional thulium fiber fractional laser treatment included melanin reduction and procollagen type-3 induction, supporting the clinical efficacy of this technique for treating photoaged skin, including melasma. Regarding

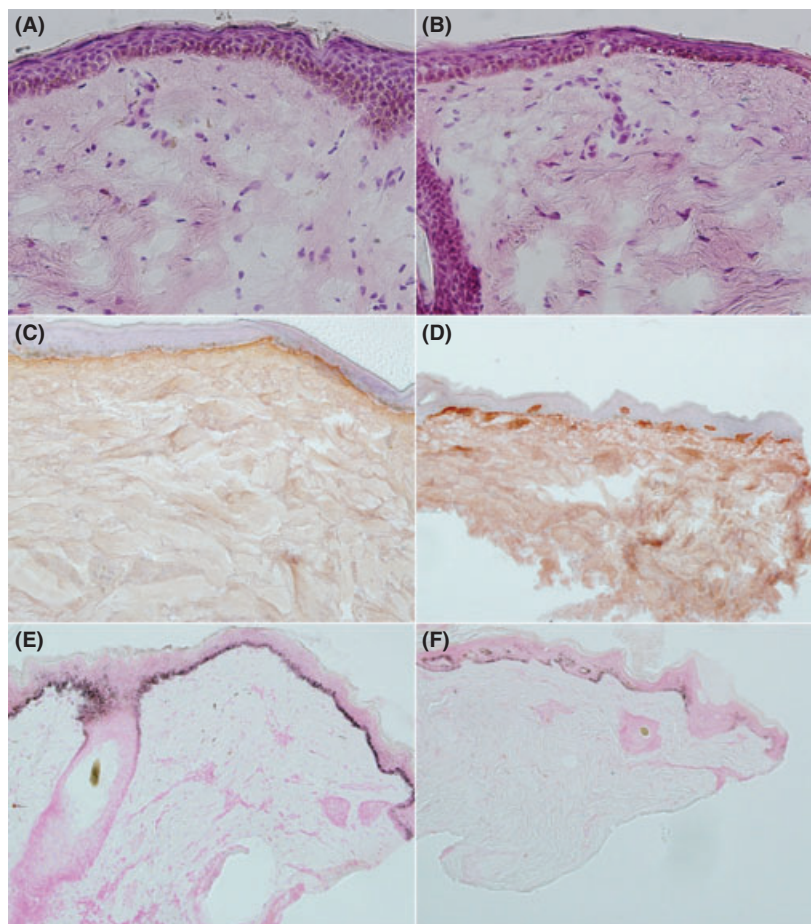


Figure 7. Histologic findings of facial skin biopsies at baseline (A, C, E) and 2 months after the final treatment (B, D, F). Collagen neogenesis was observed slightly (A and B; H&E $\times 400$ original magnification). Procollagen type-3 expression increases in the dermis after 2 months of healing (C and D; $\times 200$). Melanin decreased along the basal layer of facial skin 2 months after laser treatment (E and F; Fontana-Masson staining $\times 200$).

pigmentation such as like melasma, the 1,927-nm thulium fiber fractional laser might result in clinical improvements through MEND, which eliminates preformed melanin pigments but does not prevent melanin formation or delivery by melanocytes. We observed that Melan-A immunostaining revealed no significant change in numbers of melanocytes in treated skin sections. Thus, we suggest that intensive application of sunscreen is required to maximize clinical improvement and prevent recurrence of melasma after 1,927-nm thulium fiber fractional laser treatments. Maintenance treatment at prolonged intervals could also be helpful. Our results showed that the 1,927-nm thulium fiber fractional laser required the least patient downtime.

All participants experienced erythema and edema immediately after laser treatment that resolved within 2 days. Microcrust formation subsided within 1 week. These post-treatment reactions were easily covered with cosmetics, which enabled the patients to return to daily life immediately after the treatment. No severe adverse events such as scarring occurred. Three patients had PIH that spontaneously resolved within 3 weeks. The 1,927-nm thulium fiber fractional laser resulted in less pain than the 1,550-nm Er:glass laser (mean VAS score 4.8 vs 9.1). Our data suggest that the 1,927-nm thulium fiber fractional laser is a more tolerable and comfortable treatment modality than the 1,550-nm Er:glass laser.

Conclusion

This is the first split-face study showing the efficacy and safety of the 1,927-nm thulium fiber fractional laser treatment for photoaging and melasma in Asian skin. Histologic evidence that indicates the efficacy of thulium laser treatment support our gross observations. In conclusion, we suggest that the 1,927-nm thulium fiber fractional laser is an excellent treatment option for photoaging and melasma in Asians.

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