

Topical Application of Whitening Agents after Erbium-doped Yttrium Aluminum Garnet Fractional Laser Treatment for Melasma in Asians: A Randomized Controlled Split-face Study

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Background and Objectives

Melasma is a common hyperpigmentation disorder, which can cause refractory cosmetic disfigurement. Although fractional photothermolysis (FP) is an approved treatment for melasma, due to high relapse rates, its clinical efficacy remains controversial, especially in Asians. FP may be more useful for laser-assisted drug delivery. The objective of this study was to assess the efficacy of 2,940 nm erbium-doped yttrium aluminum garnet (Er-YAG) FP for melasma, and to compare laser treatment alone with that using laser-assisted topical whitening agents.

Materials and Methods

The faces of 12 Korean women with melasma were treated with six Er-YAG FP at 2 weeks intervals. One cheek was randomly selected for treatment with topical whitening agent after each laser treatment. The other cheek received treatment with vehicle solution. The modified melasma area severity index (MASI) and subjective physician/patient overall improvement assessments were used for measurement of outcome. These measures were recorded every two weeks during the treatment period and four weeks after the last treatment.

Results

Er-YAG FP induced clinical improvement after the third or fourth treatment, however, there was a tendency to rebound as the treatment continued. Application of a topical whitening agent after FP yielded significantly better MASI darkness, physician global assessment, and patient self assessment values than laser treatment alone.

Conclusion

Use of the Er-YAG FP laser initially resulted in improvement of melasma lesions; however, this effect was not sustained. Combination treatment comprising FP followed by application of topical whitening agent may be useful as an adjuvant option for treatment of melasma in Asian subjects, as FP may facilitate the penetration of topical drugs.

Key words

Asian; Melasma; Fractional photothermolysis; Topical drugs

INTRODUCTION

Melasma is an acquired hyperpigmentation disorder that commonly affects the facial skin. It occurs more frequently in women and can be refractory or recur frequently, particularly in Asians. Numerous treatment options have been developed, including topical bleaching agents such as hydroquinone, retinoic acid, and chemical peels. However, the efficacy of such topical agents is limited: the response to the treatment is often slow or poor, recurrence rates are high, and the rate of penetration into the skin is slow.^{1,2} Moreover, these treatments have the potential to cause skin irritation.

Recently, fractional photothermolysis (FP) was tested for its efficacy against melasma.³⁻⁷ Several pilot studies showed that FP is effective for treating melasma, and the Food and Drug Administration of the United States has approved a classical FP laser, the Fraxel[®] 1,550 nm erbium-fiber laser, for this purpose.^{6,7} However, most long-term follow-up studies on Asians showed that repetitive FP alone is followed by brief success and then a rebound.^{5,8}

Methods to improve the bioavailability of drugs in the deeper skin layers include the biomodulation of drugs and the application of physical modulation techniques, such as treatment with a fractional CO₂ laser. A fluorescence study confirmed that fractional CO₂ laser treatment facilitates the deep delivery of topical medication into the skin.⁹ However, ablative fractional erbium-doped yttrium aluminum garnet (Er-YAG) laser-assisted drug treatment may be superior to CO₂ fractional laser treatment because it may have fewer side effects (such as post-inflammatory hyperpigmentation), while they have a common therapeutic concept of ablative fractional resurfacing for drug delivery.

Thus, we performed an open-label randomized controlled split-face study to evaluate the clinical efficacy and adverse effects of fractional Er-YAG laser both with and without topical whitening agent application for the treatment of melasma in Asian women.

MATERIALS AND METHODS

Patients

Twelve Korean women with melasma were enrolled in the study. All had skin type III-IV and their ages ranged from 32 to 52 years (mean, 39.83 ± 5.80 years). Patients who were pregnant, lactating, or receiving hormone therapy were excluded. Patients who had used bleaching agents such as hydroquinone cream or who had received

laser treatment in the 6 months before enrollment were also excluded. All patients were provided with a detailed description of the purpose and possible outcomes of treatment and gave written informed consent to participate in the study. They also gave their permission for clinical photographs to be taken. This written informed consent was obtained in accordance with our Institutional Review Board-approved protocols, which respect the Declaration of Helsinki guidelines. The study was approved by the Institutional Review Board of the Asan Medical Center (Seoul, Korea).

Treatment

All treatments were performed 30 minutes after a topical anesthetic cream (EMLA[®], AstraZeneca, UK) had been applied to the face and left under an occlusive dressing. Fractional ablative photothermolysis treatment was performed using a 2,940 nm erbium-doped yttrium aluminum garnet (Er:YAG) fractional laser (ACTION[™], Lutronic, Korea) with a 250-μs pulse width. The fractional mode of this device divides pulsed light into an array of micro-beams (lens array) that each have a diameter of 250 μm and cause vertical microablative columns (density 100 spots/cm²) with variable micro-pulse energy (1-14 mJ) to form in the epidermis and upper dermis. In addition to the single shot mode, each micro-beam can be shot repeatedly, from twice to ten times, by using the 'multi shot' mode. The user can select a 9 × 9 mm or a 12 × 12 mm fractional hand piece tip. The 12 × 12 mm fractional hand piece tip was used in the present study. A single pass covers 5% of the skin. According to unpublished data provided by the manufacturer (derived from a micro-pig model), each single shot with 12 mJ of energy achieves an approximate penetration depth of 75 μm.

During each treatment session, the patient underwent one or two passes of full-face FP at energies of 12 mJ. In total, all patients underwent six treatment sessions with 2-week intervals between treatments. After the first laser treatment, one of the patient's cheeks was selected randomly and treated with a topical whitening agent (Dermaheal SB[™]; Caregen Co. Ltd, Gyunggi, Korea). The other cheek was treated with vehicle solution. The whitening product consisted of 0.6% 3-O-ethyl ascorbic acid, 0.4% arbutin, 0.4% *Glycyrrhiza uralensis* root extract, and 0.015% oligopeptide-34 in water. Ascorbic acid, arbutin, and *Glycyrrhiza uralensis* root extract are well-known whitening agents, while oligopeptide-34 is a patented agent that inhibits melanin synthesis by decreasing tyrosinase activity and reducing melanosome transfer from melanocytes to keratinocytes ([4 Medical Lasers; Engineering, Basic Research, and Clinical Application](http://www.</p>
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caregen.co.kr/anti-pigmentation05.php). After each of the remaining five Er:YAG laser treatments, the treated cheek was again treated with the topical whitening agent while the control cheek received the vehicle solution.

Evaluation

After the first treatment, the study subjects returned to the clinic every two weeks for 10 weeks (visit 2-6) and another 4 weeks after the last treatment (visit 7). The study outcomes were measured at every follow-up visit (visit 2-7). The outcome measures used in the present study were the objective melasma severity score (the modified Melasma Area and Severity Index [MASI]), and a subjective assessment of overall improvement made by the physician and the patient.

For the MASI and physician assessments, facial images were taken at all seven visits by using a Robo Skin Analyzer[®] (CS-50, Inforward, Tokyo, Japan). All images were acquired with the patient standing in the same

place under fixed illumination conditions. The Robo Skin Analyzer is a digital image analysis technology system that can quantify the area and severity of hyperpigmentation, wrinkles, and pores.¹⁰ While MASI values of the right and left cheeks have been used to quantify changes in pigmentation after treatment, the present study used the more objective modified MASI score.^{11,12}

The following formula was used: Modified MASI total score = 0.3 A(f) D(f) + 0.3 A(lm) D(lm) + 0.3 A(rm) D(rm) + 0.1A(c) D(c) (A: MASI area, D: MASI darkness, f: forehead, lm: left malar, rm: right malar, c: chin)

The total score ranges from 0 to 24. Area and darkness are scored as follows: area of involvement: 0 = absent, 1 ≤ 10%; 2 = 10-29%; 3 = 30-49%; 4 = 50-69%; 5 = 70-89%; and 6 = 90-100%. Darkness: 0 = absent; 1 = slight; 2 = mild; 3 = marked; and 4 = severe. According to this formula, MASI darkness and MASI area were subjected to statistical analysis.

The photographs were also examined by independent

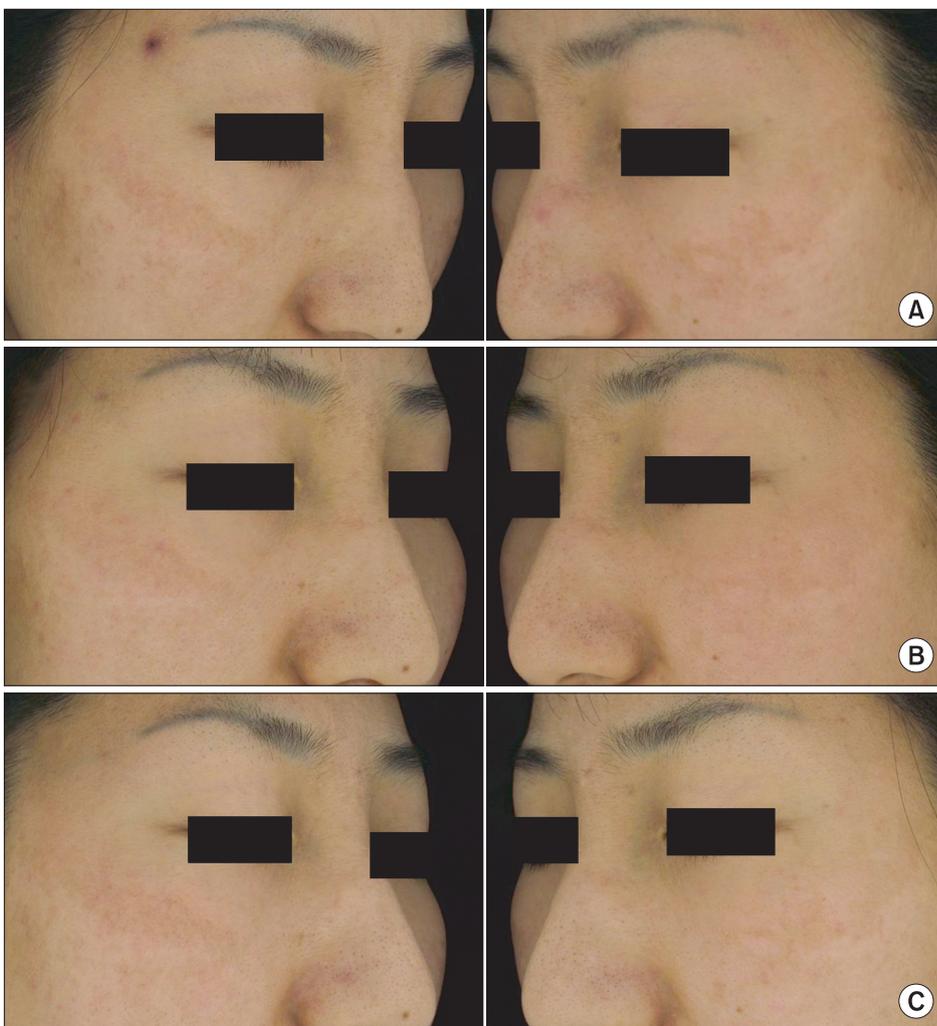


Fig. 1. Serial photographs of a 40-year-old woman with melasma before and after Er:YAG fractional laser treatment. (A) Before treatment. (B) At visit 5 (after fourth treatment). (C) At visit 7 (after sixth treatment). There was an initial improvement followed by melasma rebound after the fifth treatment. However, this was less severe on the laser-assisted topical agent-treated side (right side of this patient) than on the side that treated with the laser alone (left side).

investigators who evaluated the overall clinical skin improvement using the following 5-point scale: 0 = 0%, no improvement; 1 = 1-25% improvement; 2 = 26-50% improvement; 3 = 51-75% improvement; and 4 = 76-100% improvement. The subjective satisfaction of the patient was also rated using the following 5-point scale: Unsatisfied (0) = 0%, no improvement or worse; Slightly satisfied (1) = 1-25% improvement; Satisfied (2) = 26-50% improvement; Very satisfied (3) = 51-75% improvement; Totally satisfied (4) = 76-100% improvement.

During the study, all patients were asked to report any adverse symptoms, such as erythema, edema,

Table 1. Baseline homogeneity of outcome measures for each site

	Laser tx	Laser-assisted drug tx	p-value
	Mean ± STD	Mean ± STD	
MASI_darkness	3.00 ± 0.47	3.10 ± 0.74	0.6783
MASI_area	2.90 ± 0.99	3.00 ± 0.94	0.5911

Table 2. Longitudinal profile of clinical outcomes

Outcomes	Visit	Laser tx	Laser-assisted drug tx	p-value*
		LSMean ± SE	LSMean ± SE	
Physician assessment	2	1.40 ± 0.15	1.40 ± 0.15	0.0042
	3	2.00 ± 0.16	1.78 ± 0.16	
	4	2.51 ± 0.17	2.13 ± 0.17	
	5	2.76 ± 0.17	2.26 ± 0.17	
	6	2.51 ± 0.17	2.01 ± 0.17	
	7	2.01 ± 0.17	1.51 ± 0.17	
		<i>p</i> (2-4)**	< 0.0001	
	<i>p</i> (2-5)**	< 0.0001	0.0003	
	<i>p</i> (2-7)**	0.0092	0.6359	
Patient's assessment	2	1.40 ± 0.15	1.40 ± 0.15	0.0033
	3	2.00 ± 0.16	1.45 ± 0.16	
	4	2.38 ± 0.17	2.01 ± 0.17	
	5	2.50 ± 0.17	2.13 ± 0.17	
	6	2.25 ± 0.17	1.88 ± 0.17	
	7	1.75 ± 0.17	1.38 ± 0.17	
		<i>p</i> (2-4)**	< 0.0001	
	<i>p</i> (2-5)**	< 0.0001	0.0018	
	<i>p</i> (2-7)**	0.1211	0.9300	
MASI darkness	1	3.00 ± 0.19	3.10 ± 0.19	0.0344
	2	2.40 ± 0.19	2.90 ± 0.19	
	3	2.10 ± 0.20	2.50 ± 0.20	
	4	1.73 ± 0.21	2.32 ± 0.21	
	5	1.85 ± 0.21	2.19 ± 0.21	
	6	2.10 ± 0.21	2.57 ± 0.21	
	7	2.19 ± 0.22	2.66 ± 0.22	
	<i>p</i> (1-4)**	< 0.0001	0.0020	
	<i>p</i> (1-5)**	< 0.0001	0.0004	
	<i>p</i> (1-7)**	0.0021	0.0871	
MASI area	1	2.90 ± 0.25	3.00 ± 0.25	0.3507
	2	2.60 ± 0.25	2.90 ± 0.25	
	3	2.24 ± 0.25	2.58 ± 0.25	
	4	2.19 ± 0.26	2.50 ± 0.26	
	5	2.07 ± 0.26	2.25 ± 0.26	
	6	2.19 ± 0.26	2.37 ± 0.26	
	7	2.25 ± 0.27	2.86 ± 0.27	
	<i>p</i> (1-4)**	0.0018	0.0236	
	<i>p</i> (1-5)**	0.0003	0.0009	
	<i>p</i> (1-7)**	0.0056	0.5432	

Tx, treatment.

*Generalized Linear model: p-values for site effects.

***p* ("initial visit number"- "follow up visit number"): the value of differences between two time points.

pain, crusting, infection, post-inflammatory hyper- or hypopigmentation, and scarring.

For statistical analysis, the data obtained at each visit were analyzed using the generalized linear model in the SPSS software (version 12.0; SPSS Inc., Chicago, IL). The data are expressed as the mean±standard errors, and $p < 0.05$ was considered statistically significant.

RESULTS

Efficacy

All patients completed the six treatments. The right and left hemifaces of the 12 patients did not differ significantly in terms of average baseline MASI darkness and MASI area values (Table 1). Fig. 1 shows the serial photographs of a representative patient with melasma during the study. As shown in Table 2, the least square mean (LSMean) of MASI darkness decreased on both sides until follow-up visit 4 (after the third treatment). However, the LSMean of

MASI darkness tended to increase after follow-up visits 4-5. Overall, the laser-assisted drug-treated side showed significantly lower LSMean of MASI darkness values than the side that was treated with the laser alone ($p = 0.03$, Fig. 2). The LSMean of MASI area on both sides also dropped until follow-up visit 4-5, after which a similar rebound pattern was observed. However, the laser-alone and combination treatments did not differ significantly in terms of the LSMean of MASI area ($p = 0.35$).

In terms of clinical improvement, as assessed by the physicians, the melasma lesions on both sides of the face showed clinical improvement compared with the baseline status (Table 2). These improvements were statistically significant until after the fourth treatment, namely, on visit 5 ($p < 0.0001$ for the laser-treated side; $p = 0.0003$ for the laser-assisted drug-treated side). After the fifth to sixth treatment, the melasma lesions showed a rebound pattern. However, overall, the side treated with topical whitening agent showed better assessment scores than

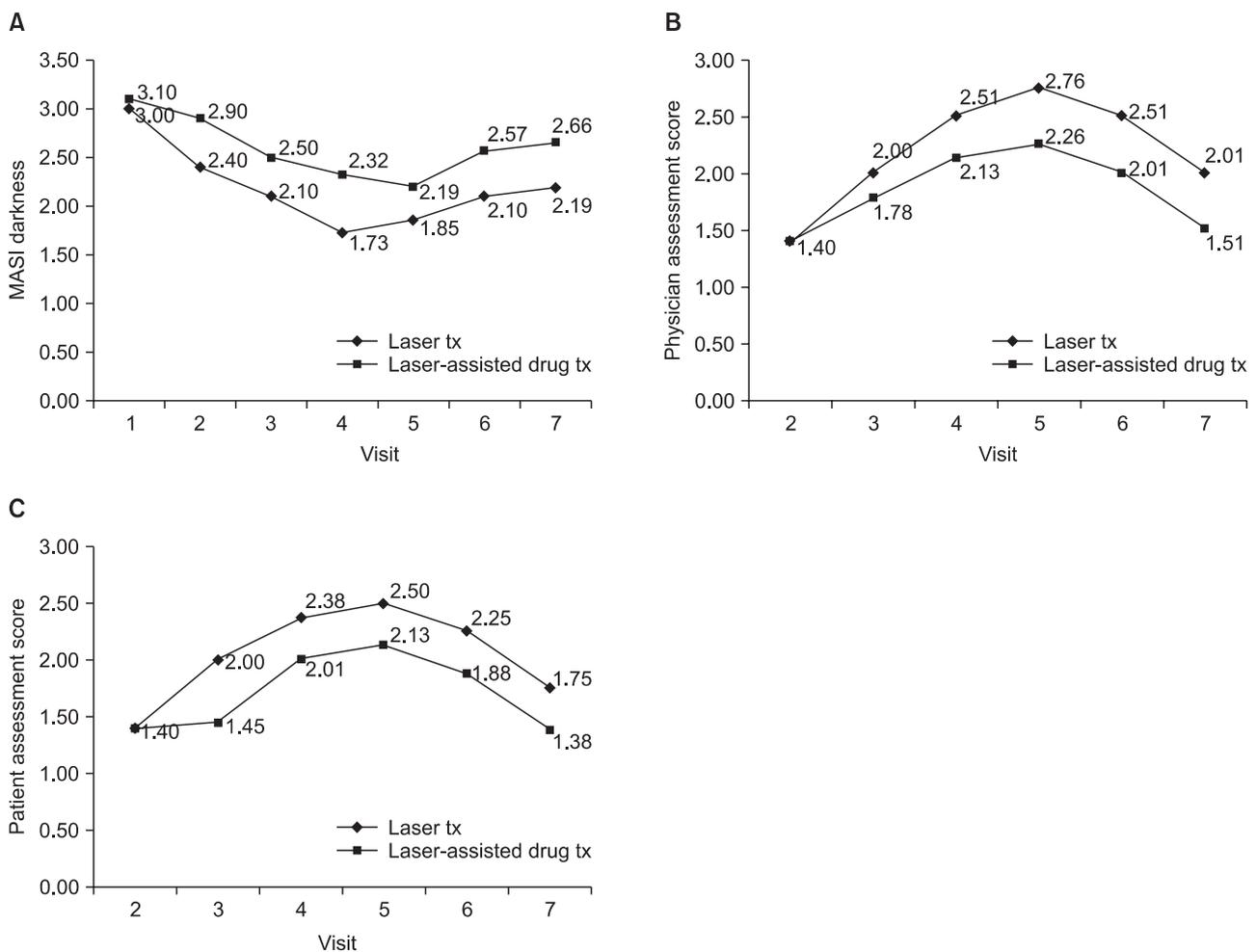


Fig. 2. Clinical outcomes based on standard photographs. (A) MASI darkness. (B) Physician assessment. (C) Patient assessment.

the side treated with Er-YAG FP alone ($p = 0.0042$) (Fig. 2).

The patient self-assessment scores paralleled the physician scores and showed similar statistical results (Table 2, Fig. 2).

Safety

All patients reported initial reactions to treatment; these reactions consisted of erythema, minimal edema, and microcrust formation on the treated areas. All patients also reported a burning sensation or mild pain; however, this gradually subsided within 2 days. Overall, the erythema and edema were mild and generally resolved within 4 days. The microcrust formation usually lasted for 1 week and then gradually disappeared. Some patients reported an itching sensation and skin dryness, neither of which required additional treatment apart from humectants. There was no evidence of *herpes simplex* infection, hypopigmentation, or scarring.

DISCUSSION

The present study examined the efficacy and safety of Er-YAG FP treatment in Asian melasma patients. The outcomes of laser-only treatment and Er-YAG fractional laser-assisted topical whitening agent treatment were also compared. Er-YAG FP initially induced a significant improvement, but a rebound effect occurred as the treatment continued. The application of a topical whitening agent after Er-YAG FP yielded better results than FP treatment alone.

Although several studies show that FP laser treatment is beneficial for melasma patients with a darker skin tone, other studies show that the initial improvement is followed by aggravation of the lesion.^{3,5,6,8} The latter findings are consistent with our own observations.

FP may have a therapeutic effect via three mechanisms. First, a FP laser-induced transport mechanism may remove epidermal and dermal melanin by incorporating it into the micro-epidermal necrotic debris.^{3,5,13} Second, FP may affect melanocytes directly by inducing thermal damage; this could reduce either their capacity to synthesize melanin or their numbers. Lastly, FP may modify the pathological dermal changes associated with melasma, such as increased levels of stem cell factors, altered fibroblasts, or greater vascularity. Recent studies suggest that these dermal changes are pathogenic factors in patients with melasma.¹⁴⁻¹⁶

Lee et al.⁵ suggested that the micro-thermal zones induced by FP must penetrate the dermis deeply enough to induce dermal remodeling if the incidence of melasma

recurrence is to be reduced. Consequently, FP treatment with higher fluence is thought to be more effective for the treatment of dermal type melasma. However, we believe that such a high energy setting may increase the risk of post-inflammatory hyperpigmentation after treatment. Therefore, present study used a drug delivery system namely, the Er-YAG fractional laser with low fluence energy. We postulate that, while the initial improvement was due to the temporary removal of cutaneous melanin, it was followed by a rebound effect because the treatment was repeated several times in relatively short period. This may have led to the accumulation of ablative damage, which in turn meant that subsequent treatments induced greater thermal damage to the dermis, although it may be much less than CO₂ laser. Thus, Er-YAG FP treatment alone does not directly inhibit melanocytes and/or the remodeling of the dermis enough to suppress melanogenesis.

In vitro studies showed that chemical agents such as arbutin, retinoids, kojic acid, licorice extract, and ascorbic acid can decrease pigment production.¹⁷ Consequently, these agents are widely used in the prescription, over-the-counter drug, cosmeceutical, and cosmetic fields. However, few of these drugs are clinically effective. Since the therapeutic efficacy of topical drugs is related to their ability to penetrate and distribute throughout the skin layers (thereby reaching the target cells), there is considerable interest in developing novel cutaneous drug delivery systems.¹⁸⁻²⁰ One such transdermal drug delivery system may be the ablative resurfacing laser. An *in vitro* study by Fang et al.²¹ reported that Er:YAG laser treatment increases the permeation of 5-aminolevulinic acid (ALA) more effectively than other delivery systems such as microdermabrasion, iontophoresis, and electroporation. Hsiao et al.²² also showed that Er:YAG laser pretreatment increased the transdermal flux of vitamin C derivatives in mice models. More recently, ablative CO₂ fractional resurfacing was shown to facilitate the delivery of a topical drug deep into the skin.⁹ The Er:YAG laser has an advantage over the CO₂ laser in that it emits a wavelength of 2,940 nm, which means that incident Er:YAG energy is almost completely absorbed by the water within the epidermis and superficial dermis; this limits the thermal damage to superficial targets and does not cause the underlying thermal damage that can be produced by the longer wavelength (10,600 nm) of the CO₂ laser.²² The present study supports the use of the Er:YAG laser for drug delivery as fractional Er:YAG laser resurfacing combined with topical whitening agent application was more

effective than fractional Er:YAG laser resurfacing alone for treating melasma.

The MASI is the most commonly used outcome measure for melasma treatment. However, its homogeneity component is difficult to assess reliably. Moreover, the area of involvement and darkness are sufficient for the accurate measurement of melasma severity.¹² Therefore, we used the modified MASI score and physician/patient global assessment to evaluate the efficacy of the treatments. MASI darkness but not MASI area showed that the combination treatment was superior to laser treatment alone in terms of delaying or reducing rebound after treatment.

The main limitations of this study were the small number of patients and the relatively short follow-up periods after the final treatment. However, to the best of our knowledge, this is the first study to compare the effect and time-course of Er-YAG FP laser-assisted topical drug delivery for the treatment of melasma. The melasma lesions in these Asian women improved significantly after the third or fourth treatment, although the lesions recurred as the FP continued. Thus, combination therapy involving the use of topical whitening agents after fractional laser treatment may be an effective adjuvant modality that reduces the relapse of melasma in Asian subjects. Future studies that assess treatment outcomes in larger cohorts of patients with epidermal and dermal melasma are needed. Moreover, the effects of laser parameters, treatment intervals, and long-term maintenance treatment should be evaluated.

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