Split-face comparative study of 1550 nm fractional photothermolysis and trichloroacetic acid 15% chemical peeling for facial melasma in Asian skin

SEUNG-PHIL HONG1,2*, SEUNG-SEOG HAN3*, SEOK-JOO CHOI1, MYOUNG-SHIN KIM1, CHONG-HYUN WON1, MI-WOO LEE1, JEE-HO CHOI1, KEE-CHAN MOON1, YOUN JIN KIM1 & SUNG-EUN CHANG1*

1Department of Dermatology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, 2Department of Dermatology, Dankook University Hospital, Cheonan, Korea, 3I Dermatology Clinic, Seoul, Korea, and 4Pureen Dermatology Clinic, Seoul, Korea

Abstract
Fractional photothermolysis (FP) therapy and chemical peels have been reported to be effective in patients with recalcitrant melasma. However, there is little information to compare the efficacy of single treatment session in Asian women. The aim of this study was to examine the efficacy, long-lasting outcomes, and safety of a single session of 1550-nm erbium-doped FP in Asian patients, compared with trichloroacetic acid (TCA) peel with a medium depth. Eighteen Korean women (Fitzpatrick skin type III or IV) with moderate-to-severe bilateral melasma were randomly treated with a single session of 1550-nm FP on one cheek, and with a 15% TCA peel on the other cheek. Outcome measures included an objective melasma area severity index and subjective patient-rated overall improvement at 4 and 12 weeks after treatment. Melasma lesions were significantly improved 4 weeks after either treatment, but melasma recurred at 12 weeks. Post-inflammatory hyperpigmentation developed in 28% of patients at 4 weeks but resolved in all but one patient by 12 weeks. There was no difference between FP treatment and TCA peeling with respect to any outcome measure. FP laser and TCA peel treatments were equally effective and safe when used to treat moderate-to-severe melasma, but neither treatment was long-lasting. We suggest that multiple or periodic maintenance treatments and/or supplemental procedures may be required for the successful treatment of melasma in Asian women.

Key Words: Asian, fractional photothermolysis, melasma, trichloroacetic acid peel

Introduction
Melasma is a hyperpigmentation disorder that typically occurs on the facial skin and is especially common in women of darker appearance, such as those of Asian, Hispanic and Middle Eastern ethnicity. The various approaches to treatment include use of sunblock agents, avoidance of exposure to the sun and employment of topical bleaching agents, such as hydroquinone, azelaic acid and tretinoin (1). However, patients are increasingly seeking more definitive and rapid treatments because melasma can be refractory or can frequently recur.

A chemical peel is the conventional treatment used for melasma patients who do not respond to topical treatment, and for patients with severe disease (1,2). Chemical peels have been particularly useful when employed to this end. Trichloroacetic acid (TCA) has been reported to be more effective than glycolic acid when used as a chemical peel, even though relapse is more common following TCA application (3). Obagi blue peel® is a chemical peel, penetrating to a superficial-to-medium depth, composed of a blue solution mixed with 15–25% TCA (4). Use of this agent makes it easier to peel skin and allows a standardized methodology to be employed.

Laser treatment such as intense pulsed light and Q-switched pigment lasers has also been used to treat melasma, but such therapy seems to show limited...
efficacy and can frequently cause inflammation, hyperpigmentation and thermal damage because of use of high-fluence radiation and bulk heating (1,5). For these reasons, the use of these devices is less recommendable. However, various recent studies have described the use of fractional photothermolysis (FP) as a treatment for melasma (6–11). The Fraxel® 1550-nm erbium-fiber laser, the most widely used laser of this type, is Food and Drug Administration (FDA)-approved for treatment of melasma. Such laser treatment minimizes thermal damage to surrounding tissue by delineating micro-treatment zones (MTZs), and by using relatively low-fluence radiation, thus permitting post-treatment epidermal healing and minimizing the risk of post-inflammatory hyperpigmentation (PIH). Moreover, both penetration depth and resurfacing area can be adjusted by control of fluence and density level, respectively. Thus, FP has been suggested to be safe and effective in the removal of both epidermal and dermal melanin and for treatment of melasma (12,13).

Although both chemical peels and laser treatments are commonly used to treat melasma, no study has compared the efficacy of single treatment session in Asian women. In the present work, we performed an open-label randomized controlled split-face experiment to compare chemical peeling using 15% (w/v) TCA, and FP treatment employing a 1550-nm laser, in Asian women with moderate-to-severe melasma.

Materials and methods

Eighteen Korean women with melasma were enrolled. All patients were of skin type III or IV; mean age (± SD) was 35.4 (± 4.67) years; and the age range was 24–45 years. Patients who were pregnant, lactating or on any hormonal therapy, were excluded. Patients who had used bleaching agents such as hydroquinone cream, or who had received laser treatment within 6 months prior to the study, were also excluded. This clinical study was approved by the Institutional Review Board of the Asan Medical Center (Seoul, Korea) and written informed consent was obtained from the patients in accordance with the "Helsinki declaration".

After 1 hour of occlusive application of a topical anesthetic (Emla® cream; AstraZeneca, Wilmington, DE), one session of FP was applied to a randomly selected cheek and 15% (w/v) TCA was used to peel the other cheek. The TCA solution (Obagi Blue Peel®; Obagi Medical Products, Long Beach, CA) was applied using three uniform coats, to penetrate the papillary dermis. A 1550-nm erbium-doped FP laser (Fraxel® SR 1500 Laser; Solta Medical, Inc., Hayward, CA) was set to a fluence of 10 mJ per MTZ, with a total density of 1320 MTZ/cm², corresponding to 20% coverage of the surface area.

Outcome measures included objective melasma severity scores and patient-rated assessment of overall improvement 4 and 12 weeks later. Facial images were obtained using a Robo Skin Analyzer® (CS-50; Inforward, Tokyo, Japan); all photographs were taken in the same location at a fixed illumination level and at a constant distance. The Robo Skin Analyzer obtains essential information on the area affected by the severity of hyperpigmentation, wrinkles, and pores, using digital image analysis (14).

Melasma Area and Severity Index (MASI) values of both cheeks were determined to quantify changes in pigmentation, as previously described (15,16). Each MASI score was objectively calculated from clinical photographs. Data were analyzed using inbuilt software of Robo analyzer by addition of the severity ratings for darkness and homogeneity, adjusted for the area treated and the percentage of the included malar region (corresponding to 30% of the total face; all treatments were applied to malar regions).

At the 4- and 12-week follow-up visits, each patient assessed her overall improvement using a visual analog scale (0–100%) and side-effects were evaluated; these included persistent erythema and PIH.

In statistical analysis, data obtained at each visit were compared with baseline information using the paired Student’s t-test and Pearson’s correlation analysis. SPSS software (version 12.0, SPSS Inc., Chicago, IL) was employed. Data are expressed as means ± standard errors, and a p-value less than 0.05 was considered statistically significant.

Results

MASI scores

Seventeen of 18 patients attended the 4-week follow-up visits, and 11 patients completed 12 weeks of follow-up. Before treatment, the mean MASI score of FP-treated cheeks was 4.96 ± 3.04 and the mean MASI score of TCA-treated cheeks was 4.94 ± 3.28 (Figure 1). Four weeks after treatment, 10 of the 17 FP-treated cheeks and 11 of the 17 TCA-treated cheeks had improved, based on a decrease in MASI score (Figure 2). The mean MASI score significantly decreased to 3.83 ± 2.05 in FP-treated cheeks and to 3.76 ± 1.94 in TCA-treated cheeks (Figure 1). However, at 12 weeks after treatment, MASI scores had risen to baseline levels, or even slightly above, in 9 of 11 FP-treated cheeks and in 10 of 11 TCA-treated cheeks (Figures 1 and 2). There was no significant difference in the mean fall in MASI score between FP- and TCA-treated cheeks at baseline, at 4 weeks after treatment or at 12 weeks after treatment (p = 0.96, p = 0.80 and p = 0.84, respectively).
Interestingly, patients with more severe baseline melasma (baseline MASI scores $\geq 4.5$) showed good responses to both treatments at week 4 but exhibited aggravated melasma at week 12. In contrast, patients with relatively mild baseline melasma (baseline MASI scores $< 4.5$) showed only slightly aggravated melasma without initial improvement during follow-up (Figure 3). In addition, initial MASI score was significantly correlated with the fall in the score at 4 weeks for both FP and TCA treatments (data not shown, $r = 0.74, p < 0.001$; $r = 0.82, p < 0.001$, respectively). Figure 4 shows serial photographs taken before and after treatment of representative patients, demonstrating an initial improvement followed by a return to pre-treatment conditions.

**Patient global improvement assessment**

At 4 weeks after treatment, 13 of 17 patients subjectively reported a reduction in their melasma. Three patients were of the view that FP treatment was more effective than was TCA treatment, whereas the other 10 patients reported that the two treatments were comparable in efficacy. Patient global assessment in terms of percentage improvement was slightly better for FP treatment than for TCA treatment (43.2% and 38.9%, respectively), but this difference was not significant (Figure 5). At the 12-week follow-up, patient assessment of improvement had significantly decreased, to approximately 25%, with respect to both treatment modalities.

**Adverse effects**

Upon treatment, patients reported tolerable mild-to-moderate pain. Mild post-treatment erythema and edema were noted, but resolved within 72 hour. Long-lasting (> 4 weeks) erythema or hyperpigmentation was evident in about 50% of patients at the 4-week follow-up, but the incidence of these conditions declined to approximately 25% at the 12-week follow-up (Table I). There was no significant difference in the level of adverse events occurring in FP- and TCA-treated cheeks. No serious adverse effect occurred, and no patient dropped out of the study because of such an event.

**Discussion**

Chemical peeling using TCA has been well-studied and is considered to be the standard treatment for melasma (16–18). The currently recommended TCA...
Figure 3. Changes in MASI score with respect to initial melasma severity. Data are expressed as means ± SDs (FP, fractional photothermolysis; TCA, trichloroacetic acid).

treatment involves application of multiple coats and/or several sessions, using a low concentration (15–20%, w/v) of TCA. TCA peeling removes melanin, rather than inhibiting melanocytes or melanogenesis, (1) and chemical peels thus yield better therapeutic outcomes when employed to treat epidermal-type rather than dermal- or mixed-type melasma (19,20).

Figure 4. Serial photographs of representative melasma patients treated with 1,550 nm fractional photothermolysis (a) and 15% (v/v) trichloroacetic acid peeling (b).

Figure 5. Patient-rated global improvement. Data are expressed as means ± SDs; n = 17 at week 4, n = 11 at week 12 (NS, not significant; FP, fractional photothermolysis; TCA, trichloroacetic acid).

Several previous studies tested the efficacy of FP laser treatment of dark-skinned patients with melasma. For example, Rokhsar and Fitzpatrick (7) found that 6 of 10 melasma patients of Fitzpatrick
skin type III or IV showed 75–100% symptom reduction after 4–6 treatment sessions performed at 1–2-week intervals. Post-treatment side-effects included 2–3 days of residual erythema and edema. Hyperpigmentation persisting through the 3-month study period was observed in only one Hispanic patient of Fitzpatrick skin type V.

Another long-term follow-up study reported that more than 50% improvement was maintained without PIH in five of eight patients of skin types II–IV for an average of 13 months after 2–7 FP (Fraxel SR®) treatments and that recurrence occurred in the other three patients (9). Interestingly, even though the cited authors did not specify patient ethnicity, all patients who maintained clinical improvement were of the same skin type (Fitzpatrick III or IV) as the patients of our study. All patients in the cited work were treated with multiple sessions (3–10) of low-energy laser energy (6–12 mJ), corresponding to 9–29% surface area coverage.

Another clinical study of melasma was recently performed on 25 Korean women (8). At 4 weeks after FP treatment (15 mJ/MTZ, density of 125 MTZ/pass, eight passes), clinical improvement was evident in 60% of patients, and 44% of patients self-reported improvement; these figures decreased to 52% and 35%, respectively, at 24 weeks after treatment. Mean melanin index fell significantly after the first two sessions, but relapsed slightly in subsequent sessions, and hyperpigmentation occurred in 3 of 23 subjects (13%). Thus, similar to our results, the cited study found a pattern of initial improvement followed by aggravation. The improvements of the cited work were more long-lasting than observed by us, presumably because multiple treatment sessions were given and greater laser fluence was used.

Three mechanisms of FP-induced improvement of melasma have been proposed. First, FP treatment may reduce epidermal and dermal melanin content by incorporation of such materials into microepidermal necrotic debris (8,9,21). Second, FP treatment may cause direct thermal damage to melanocytes, leading to a reduced capacity for melanin synthesis and/or a fall in the number of melanocytes (22). Lastly, FP treatment may modify pathological dermal changes, such as an increase in the levels of stem cell factors, alterations in fibroblasts and/or increased vascularity. Such dermal factors have been suggested to be involved in the pathogenesis of melasma (23–25).

In the present study, we used a single session of FP treatment, at low fluence (10 mJ) and moderate density. Melasma declined at 4 weeks, but recurred at the 12-week follow-up. Treatment with a 15% TCA peel led to similar results. We suggest that the initial improvement was caused by temporary removal of cutaneous melanin and that recurrence was evident because the treatment was not adequate to suppress melanogenesis via direct inhibition of melanocytes and/or remodelling of the pathologic dermal milieus.

Melasma in patients with darker skin, such as Koreans, is more difficult to treat (compared to melasma in lighter-skinned patients) because of the increased risk for recurrence or PIH. Thus, when using FP to treat melasma in Asian patients, a therapeutic approach involving multiple sessions at 4–8-week intervals, and/or additional maintenance therapies (such as use of a bleaching agent) may provide better results. Some reports have suggested that the depth of the MTZ in the dermis must be sufficient for induction of dermal remodelling, to reduce recurrence and that treatment with higher-fluence FP may be more effective in patients with dermal-type melasma (8). However, use of high-energy FP also increases the risks of PIH and aggravation of melasma.

Two previous sequential randomized studies conducted at the same institute reported that non-ablative FP at 10 mJ per microbeam was a safe and potentially useful treatment for melasma, but that a 15 mJ treatment was associated with adverse effects (10,11).

Interestingly, we found a correlation between baseline MASI score and disease progression during follow-up for both FP and TCA treatments. In other words, patients with more severe melasma tended to initially respond well to resurfacing treatment, but were also at an elevated risk of recurrence. When patients with mild melasma are treated using aggressive methods, such as FP and medium-depth TCA peeling, a cautious approach is necessary, because such treatments may aggravate melasma or cause complications without initial improvement. We propose that patients with mild melasma should be treated initially with less invasive treatments, using preventative care, bleaching agents and/or a 1064-nm Q-switched Nd:YAG laser of low fluence, rather than with aggressive procedures, as previously suggested (26).

PIH is considered to be one of the main adverse effects of resurfacing using FP or TCA peeling. In

<table>
<thead>
<tr>
<th>Adverse effect (No of treated sides)</th>
<th>Fractional laser</th>
<th>TCA peeling</th>
<th>p value</th>
<th>Fractional laser</th>
<th>TCA peeling</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent erythema</td>
<td>3 (17%)</td>
<td>4 (22%)</td>
<td>0.67</td>
<td>2 (18%)</td>
<td>1 (9%)</td>
<td>0.53</td>
</tr>
<tr>
<td>Post-inflammatory hyperpigmentation</td>
<td>5 (28%)</td>
<td>5 (28%)</td>
<td>1.0</td>
<td>1 (9%)</td>
<td>1 (9%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Total</td>
<td>8/18 (44%)</td>
<td>9/18 (50%)</td>
<td></td>
<td>3/11 (27%)</td>
<td>2/11 (18%)</td>
<td></td>
</tr>
</tbody>
</table>

Table I. Adverse effects of fractional laser and trichloroacetic acid (TCA) peeling treatments in patients with melasma.
the present study, FP and TCA treatment resulted in similar rates of adverse effects (in 28% of patients) 4 weeks after treatment, with resolution of PIH in all but a single patient at 12 weeks. Overall, none of severe PIH, persistent erythema or pain during treatment, caused significant patient distress. Thus, FP and TCA treatment both appear to be safe and tolerable treatments for melasma.

In the present work, we compared the efficacy, long-lasting outcomes and safety of one session of treatment using a 1550-nm erbium-doped fiber fractional laser, with standard 15% (w/v) TCA peeling (Obagi Blue Peel®) in Asian women. Our results indicate that the FP laser and TCA peel treatments were equally effective and safe in treatment of moderate-to-severe melasma, but that a single session of either treatment did not yield a long-lasting effect. Thus, our findings indicate that either treatment can effectively reduce melasma severity, but also suggest that multiple or periodic maintenance treatments may be required.

Acknowledgements

Funding: This study was supported by a grant of Amore Pacific Research Institute in 2010.

Declaration of interest: The authors state no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References
