Non-Ablative 1,550 nm Fractional Laser Therapy Versus Triple Topical Therapy for the Treatment of Melasma: A Randomized Controlled Split-Face Study

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Background: Melasma is a uichronic, often relapsing skin disorder, with poor long-term results from all current therapies.

Objective: To assess efficacy and safety of non-ablative 1,550 nm fractional laser therapy (FLT) as compared to the gold standard, triple topical therapy (TTT).

Study design: Twenty-nine patients with melasma were included in a randomized controlled observer-blinded study with split-face design. Each side of the face was randomly allocated to either 4–5 non-ablative FLT sessions (15 mJ/microbeam, 14–20% coverage) or TTT (hydroquinone 5%, tretinoin 0.05%, triamcinolone acetonide 0.1% cream). TTT was applied once daily for 15 weeks until the last FLT session. After this last treatment, patients were asked to apply TTT twice weekly on both sides of the face during follow-up. Improvement of melasma was assessed by patient's global assessment (PGA), patient's satisfaction, physician's global assessment (PhGA), melanin index, and lightness (L-value) at 3 weeks, and at 3 and 6 months after the last treatment.

Results: Mean PGA and satisfaction were significantly lower at the FLT side ($P<0.001$). PhGA, melanin index, and L-value showed a significant worsening of hyperpigmentation at the FLT side. At the TTT side, no significant change was observed. At 6 months follow-up, most patients preferred TTT. Side effects of FLT were erythema, burning sensation, edema, and pain. Nine patients (31%) developed PIH after two or more laser sessions. Side effects of TTT were erythema, burning sensation, and scaling.

Conclusions: Given the high rate of postinflammatory hyperpigmentation, non-ablative 1,550 nm fractional laser at 15 mJ/microbeam is not recommendable in the treatment of melasma. TTT remains the gold standard treatment. Lasers Surg. Med. 42:607–612, 2010.

Key words: Fraxel laser; topical bleaching; pigment disorder

INTRODUCTION

Melasma is a common cause of hyperpigmentation and is hallmarked by irregular brown macules on the sun-exposed parts of the face, primarily the cheeks, forehead, upper lip, nose, and chin. It frequently poses a substantial emotional and psychosocial burden on patients, and adversely affects patient's quality of life [1]. Melasma is found in all skin types but is especially seen in women with Fitzpatrick skin types IV–VI [2]. The pathogenesis is not fully understood, but genetic background and sun exposure seem to be the most important etiologic factors besides pregnancy, systemic drugs, hormonal medications, and phototoxic or photoallergic cosmetics [3].

Because of its refractory and recurrent nature, melasma is difficult to manage. Current treatments include topical bleaching creams, chemical peels, and laser therapy. However, results are often disappointing.

Treatment of choice is triple topical therapy (TTT) that was first introduced in 1975 as the Kligman formula consisting of hydroquinone (HQ) 5%, tretinoin 0.1%, and dexamethasone 0.1%. Nowadays, different concentration of

Abbreviations Used: HQ, hydroquinone; PGA, Patient's Global Assessment; PhGA, Physician's Global Assessment; PIH, post-inflammatory hyperpigmentation; SNIP, Netherlands Institute for Pigment Disorders; SPF, sun protection factor; SPSS, Statistical Package for the Social Sciences; VAS, Visual Analogue Scale.

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HQ and tretinoin are combined with various moderately potent to potent corticosteroids [4,5].

In melasma, results of lasers and intense pulsed light systems are generally disappointing and treatment is limited by adverse effects, mainly the occurrence of postinflammatory hyperpigmentation (PIH), especially in dark-skinned patients. As a result, the use of these devices is controversial [6,7].

Recently, non-ablative fractional laser therapy (FLT) at 1,550 nm was suggested as a treatment for melasma [8–10]. At this wavelength water absorption is predominant. FLT generates multiple small sized coagulated zones, separated by surrounding untreated tissue [11]. It has been suggested that these microscopic treatment zones allow transport and extrusion of microscopic epidermal necrotic debris including melanin from melanocytes through a compromised dermal–epidermal junction [11,12]. Generally, a visible wound does not appear because these microscopic treatment zones have a diameter $<100\ \mu m$ [11]. The stratum corneum was found to be intact after 24 hours [13,14]. As only part of the skin surface is treated in one session, recovery is relatively fast.

Currently, non-ablative FLT is regularly used in patients with melasma, although evidence for efficacy is poor. In a previous randomized parallel group study conducted at our institute, non-ablative FLT at 10 mJ per microbeam proved to be a safe and potentially useful alternative treatment option for melasma [10]. Given the lack of serious side effects and relative poorer clearance of melasma in skin types IV and V, optimization of laser dosimetry was suggested [10]. Moreover, a high recurrence rate was observed at 6 months follow-up. The aim of the present study was to compare non-ablative 1,550 nm FLT and TTT for the treatment of melasma in a split-face design, using more aggressive settings for FLT and long-term intermittent maintenance bleaching during follow-up.

PATIENTS AND METHODS

Study Design/Patients

A randomized controlled observer-blinded study with a split-face design was performed in 29 patients. Patients older than 18 years with Fitzpatrick skin type II–V and melasma were included from the outpatient clinic of the Netherlands Institute for Pigment Disorders at the Academic Medical Center in Amsterdam (Table 1).

The study protocol has been approved by the local medical ethics committee and registered in the clinicaltrials.gov trial register (clinicaltrials.gov identifier: NCT01085279). Written and verbal information including risks, benefits, and potential complications was given to the patients, and written informed consent was obtained. None of the patients had used bleaching creams or topical steroid creams for at least 4 weeks prior to study entry. Exclusion criteria were: history of keloid, active eczema, active acne in the face, history of facial eczema, suspected hypersensitivity to lidocaine or TTT, use of isotretinoin in the past 6 months, pregnancy, and high exposure to sunlight or UV light (UVA or UVB). Type of melasma was assessed by Wood's lamp examination [15,16]. All patients were instructed to use sunscreen (SPF 50+) every 2 hours when outside.

TABLE 1. Patient Characteristics

Male/female ratio	2:27
Mean age	41 (29–59)
Skin type	
II	6
III	12
IV	8
V	3
Melasma type*	
Epidermal	21
Mixed	8
Disease duration (years)	5 (1–17)
Oral anticonception during study	5
Previous therapy	
Corticosteroid	1
Azelaic acid	13
Hydroquinone	3
Triple topical therapy	25
Peeling	11
Intense pulsed light	1
Fractional laser therapy	4

*As assessed by Wood's lamp examination.

On the day of the first treatment each side of the face was randomly allocated to either non-ablative 1,550 nm FLT or TTT. The randomization procedure involved sealed envelopes in which the allocation was indicated. The sealed envelopes were numbered from 1 to 29. Envelopes were opened in ascending order. The randomization was based on a digitally created random list (GraphPad Software, Inc., La Jolla, CA) generated by the independent cooperator. Treatment started in March 2009 and ended in May 2009. Follow-up visits at our institute were scheduled at 3 weeks, 3 months, and 6 months after the last laser treatment. Hence, follow-up ended November 2009.

Triple Topical Therapy

In all patients, one side of the face was treated with TTT (HQ 5%, tretinoin 0.05%, triamcinolone acetonide 0.1% cream) for 15 weeks. Patients were instructed to apply cream once a day in the evening on all hyperpigmented macules of one side of the face. After this last treatment, patients were asked to apply TTT twice weekly on both sides of the face during follow-up.

Fractional Laser Therapy

The side of the face allocated to FLT was treated with a 1,550 nm Er:glass non-ablative laser (Fraxel Re:store laser, Solta Medical, Inc., Hayward, CA). One treatment session involved eight fractional laser passes to create an estimated final density of ~2,000–2,500 microscopic treatment zones per cm^2. Four passes were made in one direction and four perpendicularly. The energy per microbeam was 15 mJ. Patients with skin type II were treated during four sessions

with ~20% coverage (level 7), patients with skin types III and IV during five sessions with ~17% coverage (level 6), and patients with skin type V during five sessions with ~14% coverage (level 5). During treatment, cooling of the skin was achieved using a Zimmer Cryo 6 Cold Air Device (Phoenix Medical, Inc., Phoenix, AZ). Anesthesia consisted of topical 0.025% lidocaine and 0.025% prilocaine ointment 1 hour prior to each treatment.

Patient-Reported Outcomes

The occurrence of side effects was assessed at each FLT visit and at 3 weeks follow-up. All side effects were documented and patients were asked to score erythema, edema, crusting, and blistering on a scale from 0 to 3. Patients were asked to score the improvement of hyperpigmentation at both sides of the face separately on a visual analogue scale from 0 to 10, with 0 as no improvement and 10 as total clearance (Patient's Global Assessment, PGA). Treatment satisfaction was also scored on a visual analogue scale from 0 to 10. Furthermore, patients were asked which treatment they preferred and which treatment they would recommend to friends or colleagues. Pain was recorded on a scale from 0 to 10 after the first and third treatment.

Reflectance Spectroscopy and Melanin Index

Improvement of hyperpigmentation was assessed by color measurement through reflectance spectroscopy (Microflash 200 d; Datacolor International, Lawrenceville, GA) by a blinded investigator. This instrument, with an aperture of 4 mm, determines color by measuring the intensity of reflected light of particular wavelengths. In this study, the obtained *L*-value, indicating the lightness of the measured area of skin, was used. In addition, melanin index was measured using a chromameter (Derma-Spectrometer; Cortex Technology ApS, Hadsund, Denmark) in order to assess changes in the amount of dermal and epidermal melanin. Measurements were performed on a selected homogenous macule at both treated and control site and at normal skin before the first treatment and at follow-up.

At start, location of measurements was documented using a charcoal pencil and digital photography. The same locations were assessed at follow-up.

Physician's Global Assessment

As recommended in the guidelines for clinical trials in melasma [17], a blinded observer dermatologist assessed the Physician's Global Assessment (PhGA) as main outcome parameter using photographs that were taken under standardized conditions with a digital camera (Canon G6; Canon Components, Inc., Saitama, Japan) before treatment and at follow-up. Improvement of hyperpigmentation was scored on a scale from 0 to 6 (0: total clearance (100% improvement), 1: almost total clearance (90% improvement), 2: distinct clearance (75% improvement), 3: moderate clearance (50% improvement), 4: mild clearance (25% improvement), 5: no change, 6: worsening of hyperpigmentation) [17].

TABLE 2. Settings of Non-Ablative 1,550 nm Fractional Laser

Pulse energy	15 mJ
Level	
Skin type II	Level 7 (~20% coverage), 4 sessions
Skin types III and IV	Level 6 (~17% coverage), 5 sessions
Skin type V	Level 5 (~14% coverage), 5 sessions
Number of passes per session	8
Mean number of treatments	3.6 (1–5)
Mean energy per treatment	0.74 kJ

Statistical Analysis

Standard deviations of the difference in response of matched pairs (σ) regarding triple therapy and non-ablative fractional laser are not reported in the literature. However, we estimated that the difference would be a mean of 1 with a standard deviation of 1.5 on the PhGA scale. A sample size of 20 patients was calculated to have a power of 80% with an alpha of 0.05. To correct for potential drop out we aimed to recruit 30 patients.

Means, standard deviations, two-tailed homoscedastic Student's *t*-tests, ANOVA tests, and chi-square tests were performed with Statistical Package for the Social Sciences 16.0 (SPSS, Chicago, IL).

RESULTS

The characteristics of the 29 treated patients are listed in Table 1. Twenty-three patients completed the trial. Mean energy per laser treatment was 0.74 kJ. The laser settings are summarized in Table 2.

An intention to treat analysis was performed. Mean PGA and treatment satisfaction were significantly lower at the FLT side ($P<0.001$, Table 3). At 6 months follow-up, a significantly higher number of patients preferred TTT.

Assessment by the blinded dermatologist (PhGA) showed a significant worsening of hyperpigmentation of the FLT side compared to baseline during follow-up ($P<0.05$).

TABLE 3. Patient-Reported Outcomes

	3 weeks	3 months	6 months
Patient's Global Assessment (VAS)			
FLT	5.7 (0–10)*	4.9 (0–9)*	4.7 (0–10)*
TTT	5.0 (0–9)	5.7 (1–10)	6.1 (0–9)
Patient's satisfaction (VAS)			
FLT	5.7 (0–10)*	3.5 (0–8)*	5.3 (1–10)*
TTT	5.1 (0–8)	5.5 (1–10)	6.2 (0–8)
Advise to friends/colleagues (%)			
FLT	50	37	26
TTT	28	42	48
No preference	22	21	26

*$P < 0.001$.

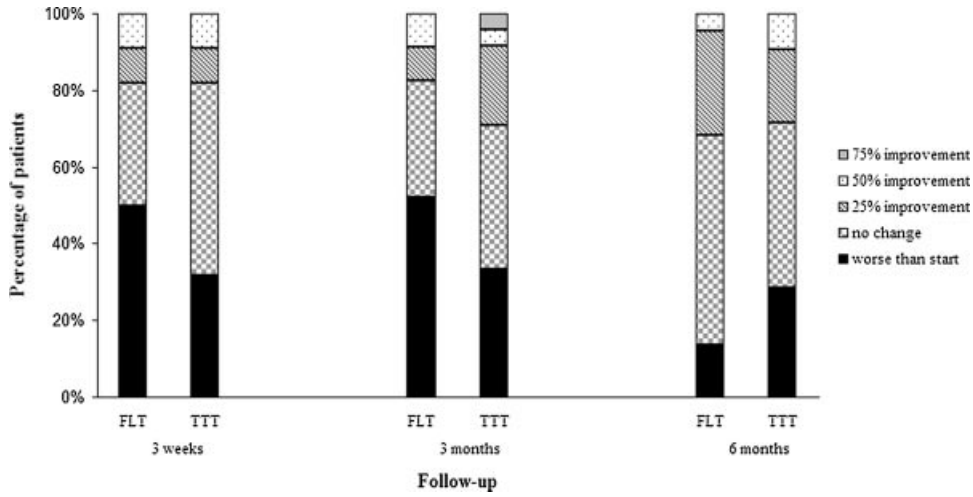

Fig. 1. Blinded physician's global assessment of non-ablative 1,550 nm fractional laser therapy and triple topical therapy during follow-up. Significant worsening of melasma was seen during follow-up at the FLT side ($F(1,18) = 7.84$, $P<0.05$).

Treatment with TTT did not result in significant changes (Fig. 1).

Melanin index and *L*-value showed a significant increase of hyperpigmentation at the FLT side compared to baseline during follow-up ($P<0.05$). At the TTT side, no significant improvement or worsening was observed.

PhGA, melanin index, and *L*-value were not significantly influenced by the use of oral anticonceptives.

Side effects at the FLT side consisted of sunburn-like erythema (99%) with an average duration of 4 days and burning sensation (86%) with an average duration of 1 day. Sixty percent of patients reported moderate-to-severe facial edema with an average duration of 2 days. Crusting and blistering were reported by 6% and 4% of patients, respectively. Patients reported an average pain score of 5.4 on a scale from 0 to 10. All patients returned to work or normal activity immediately after the laser treatment. Nine patients (31%) developed PIH at the FLT side after two or more laser treatments (Fig. 2). All these patients had Fitzpatrick skin type III or higher. PIH occurred in both epidermal and mixed type melasma with a comparable frequency (33% and 25%, respectively). Patients who developed PIH were excluded for further laser treatments. Hypopigmentation and scarring were not observed. Reported side effects at the TTT side were erythema (46%) and burning sensation (19%), which was occasionally continuous as long as treatment was applied. Forty-seven percent of patients reported scaling. One patient was forced to stop TTT after 6 weeks because of severe erythema. This patient was treated with triamcinolone acetonide 0.1% instead and later with HQ 5% and triamcinolone 0.1%.

DISCUSSION

Using 15 mJ/microbeam, non-ablative 1,550 nm FLT was not safe and effective in the treatment of melasma. Maintenance treatment at the FLT side did not result in improved clearance of melasma. At the TTT side, no significant improvement or worsening was observed. At 6 months follow-up, a significantly higher number of patients preferred TTT.

To date, there are five uncontrolled studies involving a total of 51 patients with melasma who were treated with non-ablative FLT using a 1,550 nm Fraxel Re:store laser (Solta Medical, Inc.) [8,9,14,18,19]. Only one randomized trial has been performed involving 10 patients with melasma treated with the Fraxel Re:store laser and 10 patients treated with TTT [10]. In one uncontrolled study, three patients with melasma were treated with a 1,440 nm Affirm laser (Cynosure, Inc., Westford, MA) [20]. In the studies using the Fraxel Re:store laser, settings ranged from 2,000 to 3,500 microthermal zones per cm^2 at 6–15 mJ/microbeam. The number of treatments ranged from 1 to 6. Follow-up ranged from 0 to 6 months. In one study, an improvement of 20–50% was reported by all six patients shortly after the last treatment session [18]. At 3 months follow-up, a mild to excellent clinical improvement was noted in 20 of 23 patients [9,14,20]. Furthermore, in 10 of these 23 patients, histological analysis showed a significant improvement of hyperpigmentation [14]. A remarkable improvement of melasma up to 6 months posttreatment in one patient was reported by Tannous and Astner [8]. In contrast, the two larger studies with a 6-month follow-up showed a gradual recurrence of melasma during follow-up [10,19].

The reported side effects such as erythema, burning sensation, and scaling of the TTT are well known. In our study, side effects of non-ablative 1,550 nm FLT were comparable with those reported by others. The average pain score of 5.4 is comparable with the 6.3 and 6.4 (both on a scale from 0 to 10) reported by Rokhsar and Fitzpatrick [9] and Kroon et al. [10]. However, the high rate of PIH after non-ablative

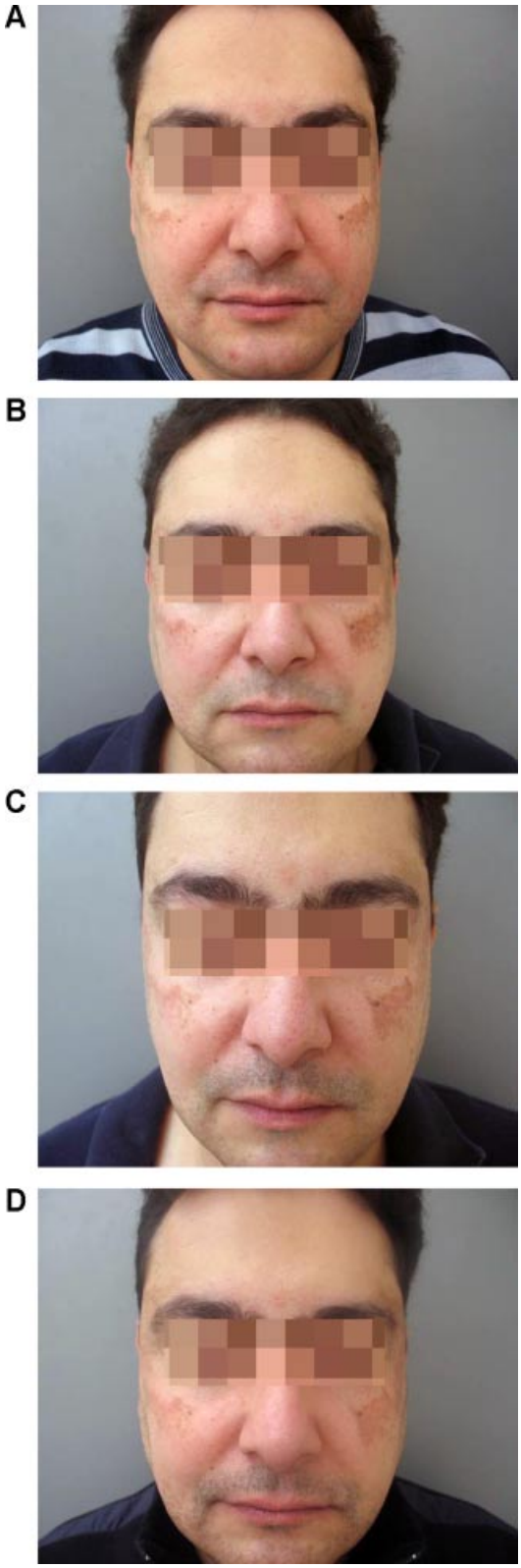

Fig. 2. Clinical photographs of a patient before treatment (**A**), at 3 weeks (**B**), 3 months (**C**), and 6 months (**D**). The right side of the face was treated with triple topical therapy for

1,550 nm FLT found in this study (31%) contrasts with the findings in other studies. In the literature, the occurrence of PIH ranges up to 17% [9,10,14,18,19]. In two studies, involving a total of 20 patients treated with non-ablative 1,550 nm FLT, PIH was not noted at all [10,14].

Non-ablative 1,550 nm FLT is widely used in melasma and the risk for development of PIH is generally thought to be minimal. However, in the present settings the risk of PIH is substantial.

Firstly, treatment in spring may have led to a high sun exposure of the laser treated site, increasing the risk of laser-induced PIH. This may partially explain the high rate of PIH, although patients were instructed to use sunscreen every 2 hours when outside. In addition, as sun exposure is a risk factor for the development and worsening of melasma, the limited efficacy of both non-ablative 1,550 nm FLT and TTT might be due to the treatment in spring and follow-up in summer.

Furthermore, the relatively high laser settings used in this study might be responsible for the occurrence of PIH. In comparison to most other studies, patients were treated with a relatively high energy per microbeam (15 mJ). Although some authors state that the occurrence of PIH is primarily determined by the density of microscopic treatment zones and not the energy per microbeam, or that it is not dependent on laser parameters at all, there are reasons to suppose that the energy per microbeam does play an important role in the development of PIH [21,22]. In a previous randomized study using the same device, we observed no PIH when treating with an energy of 10 mJ/microbeam [10]. This is in sharp contrast with our present finding of PIH in 31% of patients. It should be noted that the present study was performed in spring and an energy of 15 mJ/microbeam was applied. The latter does not necessarily lead to such a high rate of PIH. Using the same laser settings, PIH was found in 13% of 25 patients with skin type III or IV in a study by Lee et al. [19].

A minor limitation might be the effect of cooling on the efficacy and safety of non-ablative 1,550 nm FLT. Although cooling is supposed to minimize patient's discomfort during treatment, it also negatively influences the size of microscopic treatment zones and therefore compromises treatment efficacy [23,24]. Moreover, cold air cooling has been suggested to increase the risk for PIH [25].

Although TTT did not show a significant improvement during treatment and follow-up, possibly due to treatment in spring, it remains the gold standard for the treatment of melasma. There is abundant clinical experience and evidence for the efficacy of TTT in the treatment in melasma [4–7]. Costs are lower and the treatment is safer and less painful.

In conclusion, non-ablative 1,550 nm FLT is not effective in the treatment of melasma using 15 mJ/microbeam in spring time. Given the relatively high rate of PIH, caution is advocated in the usage of non-ablative 1,550 nm FLT at 15 mJ/microbeam.

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