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ORIGINAL ARTICLE

Combination of fractional erbium-glass laser and topical therapy in melasma resistant to triple-combination cream

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Abstract

Background: Melasma is a common melanosis often difficult to treat. *Objective*: The aim of this paper was to report on the safety and efficacy of non-ablative fractional photothermolysis combined with the use of triple-combination cream (TCC) on a large population with melasma resistant (i.e., with no complete/near-complete clearing) to TCC alone. *Methods*: Seventy-six patients with resistant melasma underwent a combined treatment protocol. The protocol consisted of a TCC (hydroquinone 4%, retinoic acid 0.03%, hydrocortisone butyrate 0.1%) applied daily for 10 days followed by four laser treatments performed in 3-week intervals with a fractional 1540-nm erbium-glass laser. During these intervals, and for 3 months after the last laser session, TCC was also applied daily following a "pulse-therapy" scheme. Improvement was assessed by the melasma-area-and-severity-index (MASI) score. *Results*: At 1 month, marked (>75%) and moderate (51–75%) clearing of melasma were observed in 46 of 76 (67.1%) and 12 of 76 (21%) cases, respectively. At 6 months, we noticed a marked improvement in 16 of 76 (21.1%) and no improvement in 33 of 76 (43.4%) patients. *Conclusion:* Our study proposes the combination of NFP/TCC as a useful therapy for patients with melasma resistant to TCC alone, but it shows that its long-term efficacy is limited.

Key words: *melasma, fractional laser treatment, fractional photothermolysis, hydroquinone*

Introduction

Melasma is a common acquired symmetrical facial melanosis, mostly observed in women of childbearing age with III–VI skin phototypes (1). The etiology is not fully known; however, pregnancy, oral contraceptives (OCs), genetic predisposition, and sun exposure are undoubtedly involved (2).

Available treatments for melasma, including bleaching creams, chemical peels, and lasers, are often unsatisfactory (3). The first-line therapy is the triple-combination cream (TCC) containing hydroquinone, tretinoin and steroid, which should lead – after 8 weeks – to the complete or near-complete clearing of melasma in around 25% and 50% of patients, respectively (3,4). Therefore, alternative therapy should be considered in the subgroup of patients, here termed "resistant," in whom the efficacy of TCC is limited (i.e., no complete/near-complete clearing is achieved). Recently, non-ablative fractional photothermolysis (NFP) has been used as treatment for melasma with conflicting results (5–10). Indeed, the first clinical studies reported significant improvement in melasma with this laser (6,7), and were corroborated by the decrease in melanocytes compared to the pre-treatment specimens (8). On the other hand, recent studies raise doubts regarding the thesis of NFP providing a substantial benefit in treating melasma (10), especially when compared with other conventional therapies (9,11).

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Here, we performed an open-label, single-arm study to assess the safety and efficacy of NFP combined with TCC in a large series of patients with melasma "resistant" to the sole TCC.

Patients and methods

Patient population and study design

We enrolled 78 Italian females with melasma "resistant" to TCC. This therapy consisted in a galenic cream containing hydroquinone 4%, retinoic acid 0.03% and hydrocortisone butyrate 0.1%, which was applied once a day for at least 3 months. The mean age was 35 years (range: 24–46), with a history of melasma ranging from 1 to 9 years. According to the Fitzpatrick's scale, the phototype was II in 2 patients, III in 63, and IV in 13. Sixty-eight (87%) patients complained about the appearance of melasma after an intense, natural, or artificial ultraviolet (UV) ray exposure. None of these patients suffered from endocrine or internal diseases; however, 38 patients (49%) were under therapy with OCs, 31 of whom presented melasma after the onset of OCs, and 7 reported exacerbation during OC therapy. Exclusion criteria included pregnancy, a history of keloids, or endocrine diseases, immunosuppression treatments or use of oral isotretinoin within 6 months prior to study entry.

All patients were asked to repeat the application of the previously used bleaching cream (hydroquinone 4%, retinoic acid 0.03%, hydrocortisone butyrate 0.1%) once a day, starting 10 days before each laser treatment (see below). Four days after the last laser treatment, they had to start applying the cream for 3 months, according to a pulse-therapy protocol (10 consecutive days of therapy, followed by 7 days of wash-out). They were also instructed to apply an SPF50+ sunscreen and to avoid UV exposure. Antiherpetic prophylaxis with valacyclovir 250 mg b.i.d. for 1 week was proposed to patients with a history of herpes infection, starting immediately before each laser treatment. All patients were asked to fill out a consent form, according to the Declaration of Helsinki (1989).

Laser device

The device used was a 1540-nm erbium-glass fiber laser (Lux 1540™, Palomar Medical Technologies, MA) equipped with a 15-mm handpiece (320 microbeams/cm^2, microbeam diameter 100 μm). The treatment consisted of four passes with a 50% overlap at 15-ms pulse duration and energy of 15 mJ/microbeam, achieving a final density of 3600/4000 microthermal zones/cm^2.

Safety and efficacy analysis

All patients were analyzed for side effects. To evaluate the efficacy of our therapy we used the melasma-area-and-severity-index (MASI) score (12), which is a physician-subjective measure to attempt to quantify pigmentation area, darkness, and homogeneity of melasma. The maximum score is 48 and the minimum 0. All patients were evaluated at study entry, 1 month (T1), and 6 months (T6) after the fourth and last laser treatment by two (blinded independent) dermatologists. Clinical improvement was defined as marked, moderate and mild, when the decrease of the MASI score with respect to the MASI at study entry was >75%, 51–75% and 25–50%, respectively. Worsening was defined as an increase of the MASI score ≥25%, whereas changes of the MASI score <25% were considered as irrelevant.

Statistical analysis

Data were analyzed using GraphPad Prism 5 (GraphPad Software, San Diego, California, USA, www.graphpad.com). The Wilcoxon signed rank test (a non-parametric test that compares two paired groups), the Mann–Whitney (a non-parametric test that compares the distributions of two unmatched groups), and the Kruskal–Wallis test (a non-parametric test that compares three or more unmatched group) were used as indicated; p values < 0.05 were considered as statistically significant.

Results

Seventy-six out of 78 patients completed the study, while two patients were excluded, as they had sun exposure between the laser sessions.

In all patients, as an immediate result, laser treatment caused edema for a duration of 1–3 h and erythema for 2–4 days. We observed no other side-effects.

The mean MASI score was significantly reduced 1 month (T1) after the last laser treatment (21.75 ±7.926 standard deviation (SD) *versus* 6.349 ±5.842 SD; p value < 0.0001; Wilcoxon signed rank test). Accordingly, we observed a marked (>75%) improvement in 46 of 76 patients (60.5%), a moderate (51–75%) improvement in 12 of 76 (15.8%), a mild (25–50%) improvement in 12 of 76 (15.8%), and no improvement only in 6 of 76 (7.9%) (Figures 1 and 2). There was no significant difference of the mean MASI score at study entry (T0) among the patients who presented a different degree of improvement (p = 0.9561; Kruskal–Wallis test).

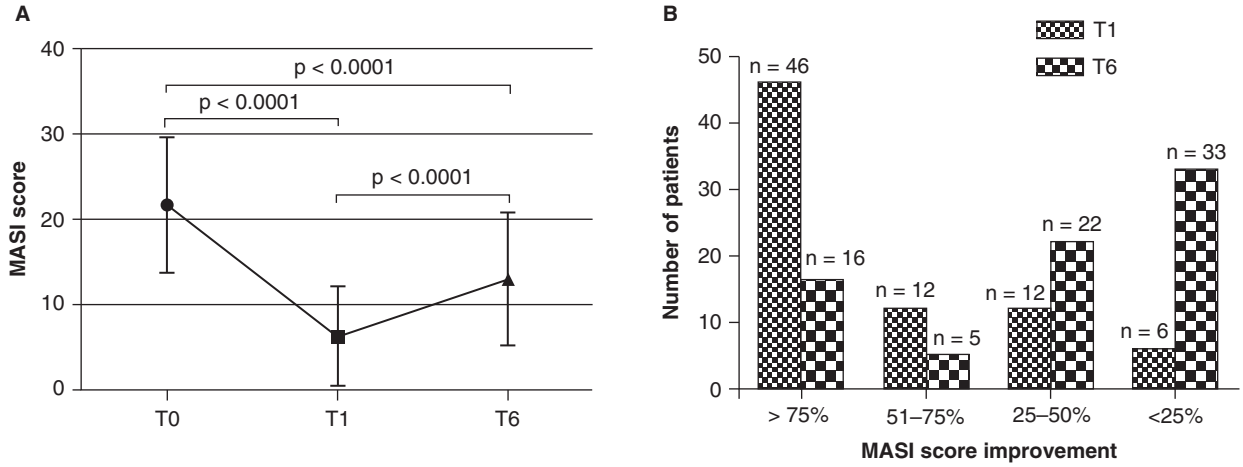

Figure 1. A: The mean MASI score (± standard deviation) at study entry (T0), 1 month (T1), and 6 months (T6) after the fourth and last laser treatment in 76 female patients with refractory melasma. B: Number of patients showing marked (>75%), moderate (51–75%), mild (25–50%), and no improvement of the MASI score at T1 and T6.

Six months (T6) after the last laser session, the mean MASI score was still significantly reduced compared to T0 (21.75±7.926 SD *versus* 13.04 ±7.822 SD; $p < 0.0001$; Wilcoxon signed rank test). However, the MASI score at T6 was also significantly increased compared to T1 (6.349 ±5.842 *versus* 13.04±7.822; $p < 0.0001$; Wilcoxon signed rank test), suggesting that the degree of the improvement is usually not maintained. Accordingly, at T6, we observed a marked improvement in 16 of 76 patients (21.1%) and no improvement in 33 of 76 (43.4%) (Figures 1 and 2). In no patient,

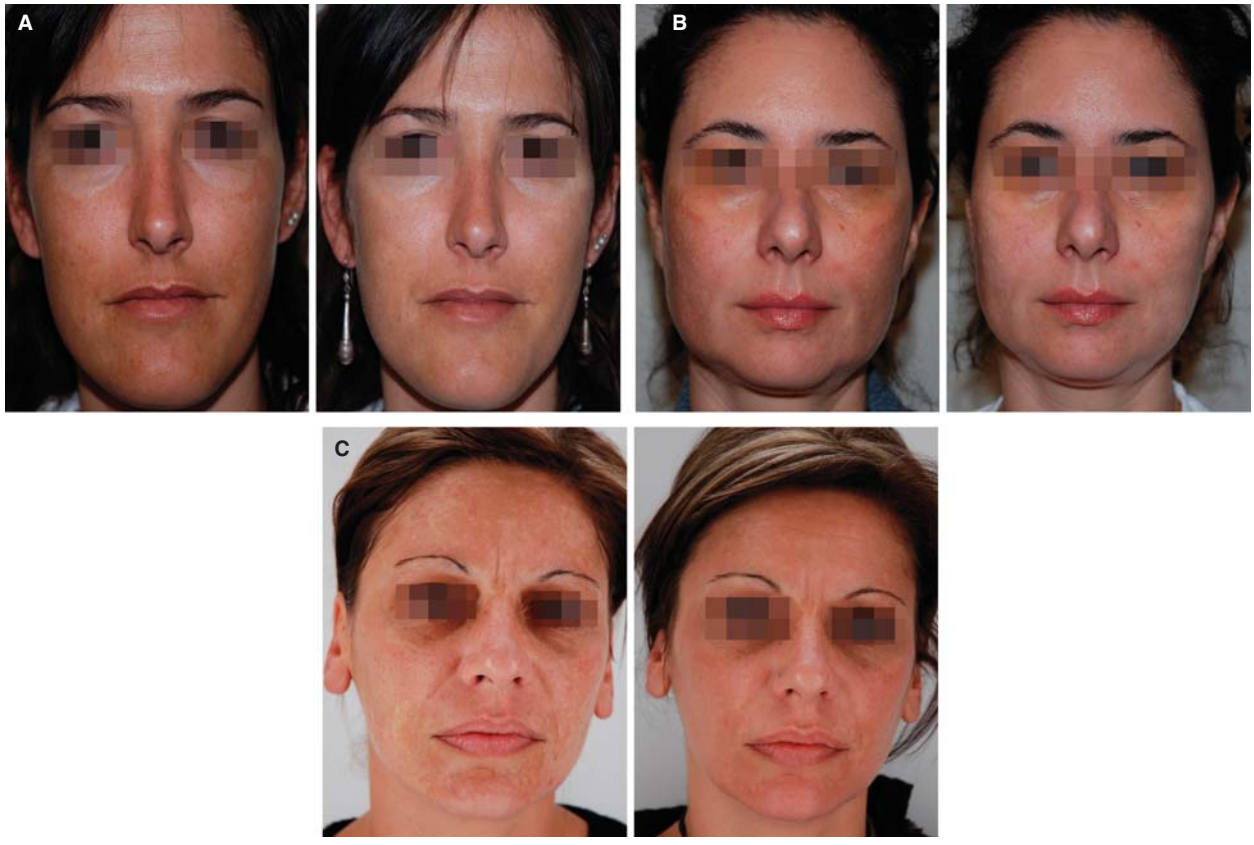

Figure 2. Examples of marked (A), moderate (B), and mild (C) improvement. Patient before treatment on the left, and 1 month after the last laser treatment on the right.

however, the melasma at T6 was more severe than at T0.

To evaluate the influence of OCs on the efficacy of our treatment, we compared the mean MASI score of the patients under OC therapy (n = 37) with the remaining patients (n = 39) at T0, T1, and T6. No significant difference was observed between these two subgroups (p = 0.2633 at T0; p = 0.8597 at T1; p = 0.8678 at T6; Mann–Whitney test).

Discussion

The combination of NFP and TCC in melasma was safe and well-tolerated. In particular, no adverse effect after NFP was noted, except for rapidly resolving edema and erythema. In contrast to some authors (10), and in agreement to others (6,13), post-inflammatory hyperpigmentation was not observed.

Regarding the efficacy, 1 month after the last laser session, we observed that 61% (46/76) of our patients had a marked improvement of melasma, which had been "resistant" to the TCC alone. Six months after the last laser session, however, a marked improvement was maintained in only 21% (16/76) of our patients. These observations suggest that in the short term, the combination of NFP and TCC is successful in the most part of cases with melasma "resistant" to the TCC alone, whereas in the long term the maintenance of a complete or near-complete clearance of melasma is limited to a smaller group of patients. The effects of our therapy were independent of the OCs.

We believe that the efficacy of our treatment in comparison to TCC alone is due to the distinct and synergic actions of the NFP and bleaching cream. Indeed, NFP leads to trans-epidermal elimination of melanin through the creation of selective columns of thermal damage (14,15), whereas the TCC prevents the formation of new melanin, thus avoiding the reappearance of hyperpigmentation (1). Moreover, NFP might favor the penetration of the TCC through the creation of channels, thus increasing its absorption.

The recurrence of melasma after 6 months from the last laser treatment further highlights the need of long-term follow-up periods to assess the maintenance of the response (3). In contrast, we are unable to establish whether a prolonged (>3 months) pulsed application of the TCC may prevent the recurrence of melasma.

The main limit of our study is that this is an open label study, where a combination therapy was used. However, all the enrolled patients presented a melasma "resistant" to TCC alone, strongly suggesting that NFP had a key role in clearing melasma. Another limit of our work, as well as for the majority of the studies in the literature, is the lack of data regarding the long-term efficacy (at least 12 months). This information is important given the relapsing nature of melasma.

In conclusion, our study proposes the combination of NFP/TCC as a logical therapy for patients with melasma "resistant" to TCC alone, but it shows that its long-term efficacy is limited.

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

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