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Assessment of Combined Fractional CO_2 and Tranexamic Acid in Melasma Treatment

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Background: Melasma continues to be a disease that is difficult to treat with no fully satisfactory results. The role of a fractional CO_2 laser in its treatment is controversial. The addition of tranexamic acid (TXA) might be helpful.
Objectives: To assess the efficacy of a low-power fractional CO_2 laser alone versus its combination with tranexamic acid used either topically or intradermally for melasma treatment.
Methods: A randomized comparative split-face study included a total of thirty female patients with bilateral, symmetrical melasma. The whole face was subjected to treatment via a low-power (12 Watts) fractional ablative CO_2 laser. One side was randomly assigned to topical application of tranexamic acid solution after the session immediately or intradermal microinjection of tranexamic acid prior to the laser session. Sessions were conducted every 4–6 weeks for five consecutive sessions. Assessments were done using the melasma area severity index MASI score, melanin index (MI), and erythema index (EI) before sessions and 2 weeks after the final session.
Results: After treatment, there was significant reduction in the MASI score on both sides of the face; the side treated with the fractional CO2 laser alone and the side treated with fractional CO_2 laser combined with TXA (topically or intradermal injection) (P-values 0.007, <0.001, and 0.016, respectively). MI was significantly lower on the side receiving fractional CO_2 laser alone and the side receiving fractional CO_2 laser combined with intradermal injection of TXA (P-values <0.001 and 0.003, respectively), while the EI showed significant improvement only on the side receiving fractional CO_2 laser alone (P-value $= 0.023$). Although patients reported no differences in improvement on either treated side, the degree of improvement regarding the MASI score was better on the side receiving fractional CO_2 laser alone. Regarding MI, the degree of improvement was higher on the side receiving fractional CO_2 laser combined with intradermal injection of TXA than on the side receiving fractional CO_2 laser alone; however, this improvement did not reach statistical significance. Minimal complications occurred in the form of mild pain.
Conclusion: A low-power fractional CO_2 laser is an effective, safe treatment for melasma. However, the addition of tranexamic acid (either topically or intradermally) to a fractional CO_2 laser should be further studied. Lasers Surg. Med. 51:27–33, 2019. © 2018 Wiley Periodicals, Inc.

Key words: fractional CO_2 laser; melasma; tranexamic acid

INTRODUCTION

Melasma is a common acquired skin disorder that is characterized by dark, brown symmetrical patches of hyperpigmentation involving the sun-exposed areas of the face [1]. The mechanism of melasma has yet to be fully elucidated; however, current research suggests it is a multifactorial condition in which pathways of pigment homeostasis are disrupted in the epidermis, extracellular matrix, and dermis [2]. These changes lead to melanosome accumulation at the dermo-epidermal junction (DEJ), the papillary dermis, or deeper layers [3].

The treatment of melasma remains a challenge. Laser and light therapies may be utilized cautiously as second-line or third-line options for recalcitrant melasma; however, low-energy settings are preferred due to the risk of post-inflammatory hyperpigmentation and melasma stimulation [4].

The development of fractional resurfacing has led to improvements to melasma treatment with decreased incidence of post-inflammatory hyperpigmentation; these improvements are due to the enhanced healing times and decreased inflammation as a result of the formation of microscopic columns of tissue destruction. These microscopic columns of damaged tissue are surrounded by areas of normal tissue, allowing for shorter migratory paths for the healing keratinocytes [5].

Tranexamic acid (TXA), a plasmin inhibitor, has been suggested as an effective treatment for melasma, with promising results [6]. TXA used in several forms, including oral [7], topical [8], and localized microinjection forms [9], where it has been shown to improve melasma.

The aim of this study was to assess the efficacy of a low-power fractional CO_2 laser for the treatment of melasma

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.
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versus its combination with tranexamic acid, whether used topically or injected intradermally, and to evaluate possible complications of the procedure.

PATIENTS AND METHODS

A total of 30 patients were enrolled in the study. Patients were recruited from the dermatology out-patient clinic, Kasr Al-Ainy University teaching hospital, Cairo University, after approval of the study by the local ethical committee. The study was performed from February 2016 to June 2017. Informed written consent was obtained from patients prior to the study.

Patients with bilateral symmetrical facial melasma above 18 years old were included in the study. Wood's lamp examination was performed and patients with mixed-type melasma were included.

The exclusion criteria were as follows: pregnancy and lactation, patients taking oral contraceptive pills, or hormonal replacement therapy at the time of the study or during the past 12 months, concomitant use of anticoagulants, bleeding disorders, scarring and keloid tendency, active skin infections and active HSV, history of photosensitivity or photosensitizing medications such as sulfonamides and tetracycline, and previous history of post-inflammatory hyperpigmentation.

Study Design

This was a randomized, split-face, comparative study. All patients received full-face low power (12 Watts) fractional ablative CO_2 laser treatments. One side of the face was randomly assigned to the addition of TXA either topically or intradermally. Randomization was carried out by patients drawing closed sealed envelopes containing cards with treatment code TXA topical right, TXA intradermal right and *vice versa*.

Laser Treatment

Topical anesthetic cream (lidocaine 25% and prilocaine 25%) (Pridocaine®) was applied for an hour prior to the laser session and wiped off just prior to the session. Five consecutive sessions, 4–6 weeks apart, were performed by fractional CO_2 laser (DEKA, SMARTXIDE DOT, Italy) using the following parameters: power 12 Watts, spacing 800 μm (7.3% density), dwell time 300 microseconds, stack 1, and frequency of 1 Hz.

TXA Application

Topical application of tranexamic acid solution was applied after the session immediately (Kapron 500 mg/5 ml ampoules, Amoun Pharmaceutical Company), while intradermal injection of tranexamic acid was performed prior to laser session. A 1.0-ml syringe with 100 mg/ml TXA was prepared under sterile conditions. Injections were applied intradermally on melasma areas at 1-cm intervals.

Patients were advised to avoid excessive sun exposure and to apply a broad-spectrum sunscreen and emollients for 1 week post-procedure. Assessment was done by two blinded dermatologists before every session and 2 weeks after the last session.

Follow-up was done by:

(1) Photographs that were taken using a high-resolution digital camera (Nikon Coolpix S2900, 20.1 Megapixel) at each visit and 2 weeks after the last session.
(2) Melasma Area and Severity Index (MASI) score.
In this scoring system [10], the whole face is divided into four areas: the forehead, right malar, left malar, and chin, corresponding to 30%, 30%, 30%, and 10% of the total face area, respectively. The grade of melasma severity was determined by three variables: the percentages of total area involved, on a scale of 0 (no involvement) to 6 (90–100% involvement); darkness, on a scale of 0 (absent) to 4 (maximum); and the homogeneity of hyperpigmentation, on a scale of 0 (minimal) to 4 (maximum).
MASI score was calculated on each side of the face by a blinded scorer at baseline and after the last session by 2 weeks by the equation:

$$\begin{aligned}\mathrm{MASI} = {} & 0.3\ (\mathrm{DF} + \mathrm{HF})\ \mathrm{AF} + 0.3\ (\mathrm{DMR} + \mathrm{HMR}) \\ & \mathrm{AMR} + 0.3\ (\mathrm{DML} + \mathrm{HML})\ \mathrm{AML} \\ & +0.1\ (\mathrm{DC} + \mathrm{HC})\ \mathrm{AC}\end{aligned}$$

where D is darkness, H is homogeneity, A is area, F is forehead, MR is right malar, ML is left malar, and C is chin. The values 0.3, 0.3, 0.3, and 0.1 stand for the three parameters' percentage of total facial area. Maximum MASI score for the total face was 48, and on each side of the face, it was 24.
(3) The melanin index (MI) and erythema index (EI) was measured using a reflectance spectrophotometer (Dermacatch, Colorix, Neuchatel, Switzerland) in order to assess the degree of hyperpigmentation, before and after the last session [11]. It uses a single monochromatic source to measure surface reflectance intensities. It does not provide colorimetric values but rather erythema and melanin indices of the surface.
(4) The patient's self-assessment. The patients' self-assessment of melasma improvement was graded along four scales: more than 75% lightening (excellent); 51–75% (good); 26–50% (fair); and 0–25% (poor).

Complications were recorded during the study period. These complications included post-inflammatory hyperpigmentation (PIH), prolonged erythema, acne and milia, contact dermatitis, delayed purpura, HSV reactivation, scarring, and keloid formation.

Statistical Methods

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 24. Data were summarized using mean, standard

TABLE 1. Demographic Data of Patients Summarized

Data	Fractional CO_2 laser alone	Fractional CO_2 laser + topical TXA	Fractional CO_2 laser + intradermal TXA
Number of patients	28	13	15
Gender			
Males	0	0	0
Females	28 (100%)	13 (46.4%)	15 (53.6%)
Age (years) (mean ± SD)	39.61 ± 6.71	40.45 ± 8.23	38.80 ± 5.21
Duration (months) (mean ± SD)	6.321 ± 4.40	8.230 ± 4.86	4.666 ± 3.28
Fitzpatrick skin type			
III	14	6	8
IV–V	14	7	7

deviation, median, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were made using the non-parametric Kruskal-Wallis and Mann-Whitney tests. For comparison of serial measurements (before and after) within each patient the non-parametric Wilcoxon signed rank test was used. For comparing categorical data, the chi square (χ^2) test was performed. The exact test was used instead when the expected frequency was less than 5. Correlations between quantitative variables were examined using the Spearman correlation coefficient. *P*-values less than 0.05 were considered statistically significant (Table 1).

RESULTS

Clinical Assessment of Melasma Before and After Treatment

Only 28 patients completed the study. Two patients from the topical TXA group dropped out due to the occurrence of post-inflammatory hyperpigmentation. On the side of the face receiving fractional CO_2 laser alone, the mean MASI score, the mean MI and the mean EI were significantly lower after treatment (*P*-values $<0.001^*$, $<0.001^*$, and 0.023^*, respectively).

On the side of the face receiving fractional CO_2 laser and topical TXA, only the mean MASI score was significantly reduced (*P*-value 0.007^*). Regarding the side receiving fractional CO_2 and intradermal injection of TXA, statistically significant reductions in MASI score and MI were detected (*P*-values 0.016^* and 0.003^*, respectively). The results are illustrated in Figures 1–3 and in Table 2. When comparing the three modalities together with respect to MASI, MI, and EI after treatment, no statistically significant difference was detected (*P*-values 0.515, 0.69, and 0.588, respectively).

Comparing the Degree of Improvement Among the Three Treatment Modalities

The degree of improvement (the difference between pre- and post-treatment values) regarding the MASI score and EI was better on the side receiving fractional CO_2 laser alone, followed by fractional CO_2 laser and topical TXA, then fractional CO_2 laser and intradermal TXA.

Regarding MI, the degree of improvement was higher on the side receiving fractional CO_2 laser combined with intradermal injection of TXA with (mean ± SD) (27.40 ± 26.62) than on the side receiving fractional CO_2 laser alone (25.75 ± 32.63) or the side receiving fractional CO_2 and topical application of TXA (18.69 ± 33.43).

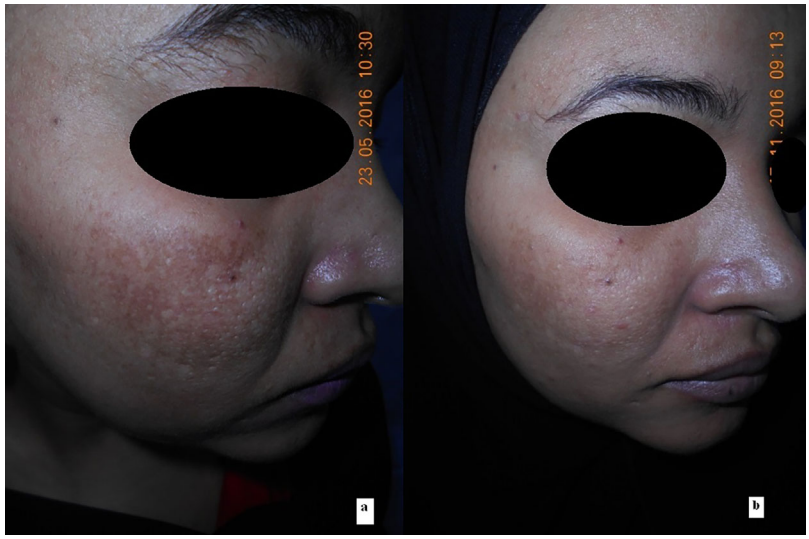

Fig. 1. Fractional CO_2 laser alone pretreatment (**a**) and post-treatment (**b**).

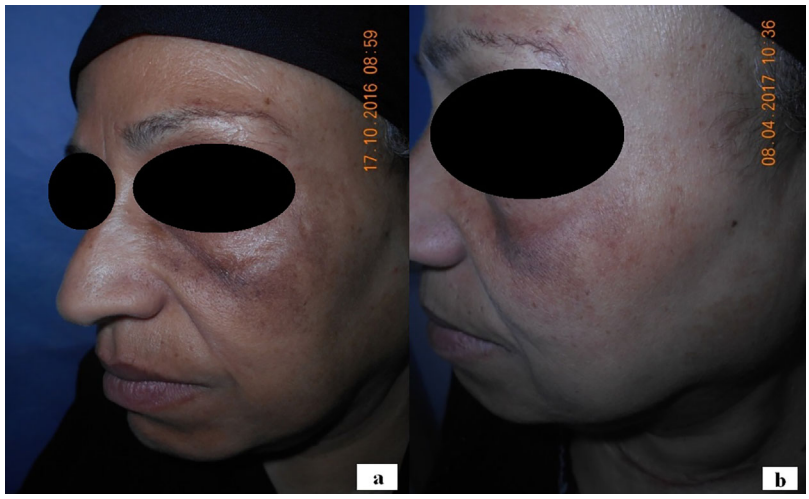

Fig. 2. Fractional CO_2 laser with topical TXA pretreatment (**a**) and post-treatment (**b**).

Nevertheless, this improvement did not reach statistical significance. The results are illustrated in Table 3 and in Figure 4.

Comparing the Three Modalities as Regards Patients' Satisfaction

Patient satisfaction did not differ among the used three treatment modalities (*P*-value 0.879).

Assessment of Complications

All 28 patients (100%) reported mild burning pain after the sessions that lasted for few hours. Only two patients randomized to the topical TXA group among the enrolled 30 patients (6.7%) discontinued treatment after the first session due to occurrence of post-inflammatory hyperpigmentation.

DISCUSSION

The present study showed that fractional CO_2 laser provided measurable improvement in the clinical appearance of melasma as well as reduction in both melanin and erythema indices.

The microepidermal necrotic debris (MEND) extruded after fractional thermolysis contains melanin, as shown in the histological findings of Rox Anderson's lab [12]. The MENDs are proposed to act as "melanin shuttles" that lead to depigmentation of the epidermal and dermal layers by means of packaging excess melanin that are then eliminated through the stratum corneum [13]. Moreover, there is a redistribution of melanin between areas of untreated skin and treated skin, resulting in an overall decrease in the hyperpigmented appearance of the skin [14].

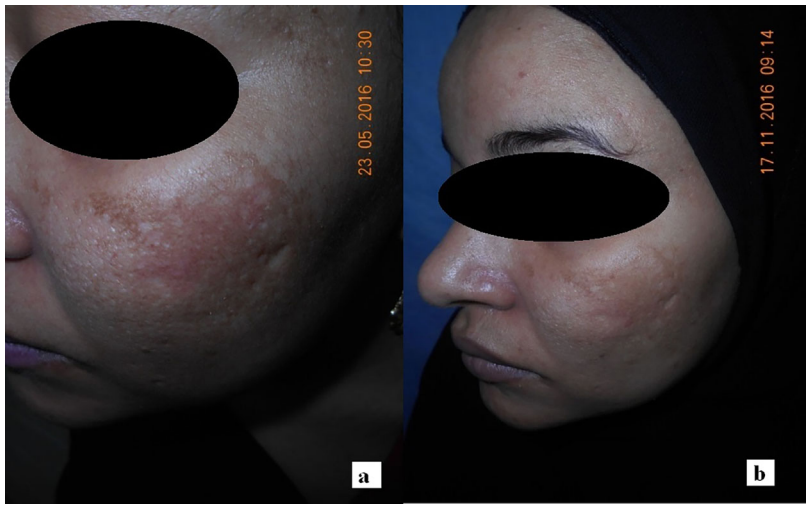

Fig. 3. Fractional CO_2 laser with intradermal TXA pretreatment (**a**) and post-treatment (**b**).

TABLE 2. Response to Treatment Among the Three Modalities

Clinical assessment	Fractional CO_2 laser alone			Fractional CO_2 laser + topical TXA			Fractional CO2 laser + intradermal TXA		
	Pre-treatment (mean ± SD)	Post-treatment (mean ± SD)	*P*-value	Pre-treatment (mean ± SD)	Post-treatment (mean ± SD)	*P*-value	Pre-treatment (mean ± SD)	Post-treatment (mean ± SD)	*P*-value
MASI	7.00 ± 4.74	5.25 ± 3.90	<0.001*	6.71 ± 4.69	5.02 ± 3.05	0.007*	5.86 ± 4.82	4.41 ± 4.19	0.016*
MI	627.18 ± 56.25	601.43 ± 48.50	<0.001*	635.38 ± 51.23	616.69 ± 56.27	0.065	626.33 ± 53.06	598.93 ± 43.55	0.003*
EI	449.64 ± 10.86	444.43 ± 11.12	0.023*	451.69 ± 10.33	446.85 ± 11.15	0.675	446.67 ± 11.02	443.07 ± 11.81	0.105

*P-value (significant if <0.05).

This was similar to results of several studies. Trelles et al. [15] reported that melasma patients who underwent combined treatment with CO_2 laser and long-term topical lightening cream showed the greatest improvement and were able to maintain treatment benefits up to 12-month post-treatment.

Neeley et al. [5] described a case report of a 59-year-old female who showed good improvement after 7 sessions of fractional CO_2 laser over 10 months but did not respond previously to 17 sessions of non-ablative fractional laser.

In 2014, Jalaly et al. [16] concluded that low-power fractional CO2 laser was more effective in lowering the MASI score with few side effects, with the advantage of almost no downtime requirement for wound-healing compared with Q-Switched 1064 Nd-YAG laser.

One unifying concept in all the laser and light therapies that have been tested so far is the synergism between topical anti-tyrosinase treatment and the laser and light procedure. In general, pretreatment and post-treatment topical regimens in conjunction with laser and light treatments help reduce the risk of rebound hyperpigmentation, post-inflammatory pigmentation, and increase the longevity of the lightening effect on melasma [3]. To the best of our knowledge, this is the first study comparing low-power fractional CO_2 laser alone versus its combination with TXA topically or intradermally.

TXA was first reported for the treatment of melasma in Japan by Nijo in 1979 [17]. The mechanism of action of TXA on melasma may be by decreasing UV-induced pigmentation by blocking melanin synthesis in melanocytes by inhibiting plasmin-plasminogen system, interfering with the interaction of keratinocytes and melanocytes [18,19].

TXA is a plasmin inhibitor that also suppresses angiogenesis and prevents neovascularization induced by basic fibroblast growth factor (b-FGF) [20]. TXA also decreases the activity of mast cells [21]. In the present study, there was no significant difference in EI with addition of TXA to laser treatment. We hypothesized that this may be attributed to the triggering of an inflammatory response by the topical or intradermal application of tranexamic acid following fractionated CO_2 laser; thus, a longer follow-up period might improve the results.

Fractional CO_2 laser and intradermal TXA injection produced a significant reduction in MASI score and MI, suggesting that intradermal microinjection of TXA might be a better combination than topical because of direct introduction of the drug into the skin.

Kanechorn et al. in 2012 [8] studied the use of 5% TXA in a liposome gel formulation for epidermal melasma for a duration of 12 weeks. Even though 78.2% of patients showed a decrease in the melanin index, the results were not significant compared with the vehicle, and the former induced erythema in many subjects. Newer topical preparations of TXA acetyl ester HCl might prove helpful in reducing erythema and the stinging sensation experienced by some patients.

Kondou et al. [22] successfully employed topical TXA emulsion for the treatment of melasma and freckles for

TABLE 3. Comparing the Degree of Improvement Among the Three Treatment Modalities

	Fractional CO_2 laser alone	Fractional CO_2 laser + topical TXA	Fractional CO_2 laser + intradermal TXA	*P*-value
Degree of improvement in MASI (mean ± SD)	1.75 ± 2.15	1.70 ± 2.62	1.45 ± 1.89	0.933
Degree of improvement in MI (mean ± SD)	25.75 ± 32.63	18.69 ± 33.43	27.40 ± 26.62	0.715
Degree of improvement in EI (mean ± SD)	5.21 ± 11.73	4.85 ± 16.37	3.60 ± 7.85	0.728

5–18 weeks. It was reported that topical TXA also prevented the appearance of new lesions.

In the present study addition of topical TXA to laser improved the appearance of melasma but with no statistically significant difference than laser alone. This may be attributed to the number of patients enrolled in the study and to the method of administration of TXA that was only prior and immediately after laser sessions, in contrast to other studies that used TXA for melasma treatment more frequently.

Ebrahimi and Naeini [23] conducted a prospective, randomized, double blind split-face trial of 50 Iranian patients comparing TXA versus hydroquinone plus dexamethasone and concluded that topical solution of TXA appeared to be a potentially new medication that can lead to quite rapid results without significant and serious side-effects for melasma, especially for the epidermal type.

Lee et al. [24] conducted a prospective open pilot study wherein they treated melasma with localized intradermal microinjections of tranexamic acid repeated weekly for 12 weeks. A significant decrease in MASI from baseline to 8 and 12 weeks was observed. They concluded that intralesional microinjection of TXA acid was a potentially new, effective, and safe therapeutic modality for the treatment of melasma.

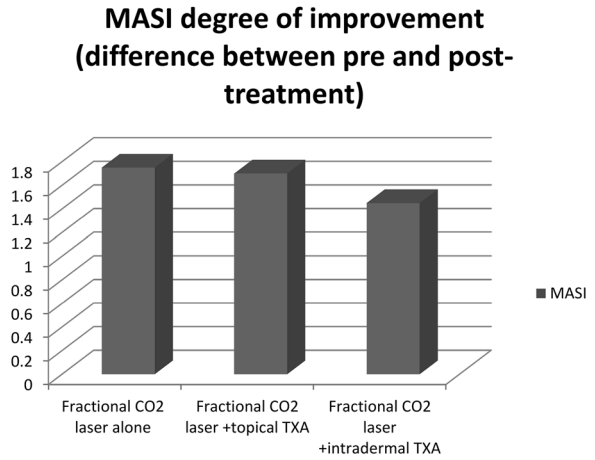

Fig. 4. Degree of improvement among the three treatment modalities regarding MASI score.

Budamakuntla et al. [9] in a prospective randomized open label study comparing the effect of TXA microinjections versus microneedling in melasma patients, reported better improvement in patients treated with microneedling than with microinjections; however, this difference was not statistically significant, suggesting that TXA intradermal microinjection and microneedling are office-based procedures with relatively quick results, no significant side-effects and almost no downtime.

In this study two patients randomly assigned to topical TXA group dropped out due to the occurrence of complications in the form of post-inflammatory hyperpigmentation. This could be attributed to improper sun protection after treatment sessions, which is why strict sun protection precautions are very important to adhere to after fractional laser treatments especially in patients of darker skin types or in those prone to melasma.

In the current study, patients were satisfied with the results with no statistically significant difference among the three modalities of treatment, suggesting that low-power fractional CO_2 laser was effective in melasma treatment. Addition of TXA could add better results if the drug was applied more frequently.

In our study, patients were not able to distinguish the differences in degree of improvement in pigmentation between both sides of the face, and the patient satisfaction scale was the same for both sides with no statistically significant differences.

This was similar to the study conducted by Trelles et al. [15], which compared topical melasma cream (Kingman's formula), CO_2 ablative fractional resurfacing and a combination of both. Patients in the combination group were more satisfied (70% satisfaction index).

Jalaly et al. [16] reported different results regarding the patient satisfaction in evaluation of the low-power fractional CO_2 laser for melasma treatment.

Furthermore, Kanechorn et al. [8] and Lee et al. [24] reported similar results to those of our study with respect to patient satisfaction. No serious side-effects on either side of the face were reported, except for pain or slight discomfort after the sessions.

CONCLUSION AND RECOMMENDATIONS

Low-power fractional CO_2 laser is an effective, safe treatment for melasma. However, addition of tranexamic

acid to fractional CO_2 intradermally should be further studied, as it might have an added effect over sole therapy.

When tranexamic acid is used intradermally, it should be alternated with fractional CO_2 laser and not used in the same setting, in order to reduce the added inflammatory reaction elicited when both modalities are combined, which in turn leads to decreased effectiveness in the treatment of melasma.

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