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Original Article

Therapeutic approaches for refractory melasma: Fractional CO_2 Laser and Q-Switched Nd:YAG Laser with tranexamic acid injections

Sara Ahmed Ali

Department of Dermatology, College of Medicine, University of Al-Qadisiyah, Diwaniyah city, Iraq.

Abstract

Background Melasma is characterized by dyspigmentation that is difficult to treat. This is due to the complex underlying factors and high risk to recurrence.

Objective Investigating the clinical outcomes from utilizing fractional CO2 laser and Q-Switched Nd:YAG laser (QSNY) in combination with tranexamic acid (TA) in treating refractory melasma.

Methods The cross sectional study included sixty women with refractory melasma. Patients were randomly assigned into two groups (30 patients per group) to receive either the fractional CO2 laser or the QSNY laser treatment. Patients from both groups were supplemented with intradermal microinjections of TA (4 mg/ml), and laser sessions were conducted every month for a total of four successive sessions per patient. Treatment outcomes were assessed via calculating modified melasma area and severity index (mMASI) at baseline and after 30, 60, 90, and 120 days of post-treatment.

Results There was a significant reduction in mMASI score (p<.001) after each therapy session. The fractional CO2 laser with TA demonstrated higher efficacy in reducing mean mMASI score (1.98±1.0) relative to the Nd-YAG laser with TA (3.1±1.5), (p<.001). Although the clinical effectiveness of fractional CO2 laser with TA was higher, patient satisfaction among study groups were found with no significant difference (p>.05).

Conclusion Fractional CO2 laser and QSNY laser treatments in combination with intradermal TA injections are effective approaches in decreasing the overall mMASI scores in women with refractory melasma. Further studies are necessary to enhance our understanding and to guide optimal clinical practice regarding refractory melasma.

Keywords Refractory melasma; Fractional CO2 laser; QSNY laser; tranexamic acid.

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Introduction

Melasma is a common skin disorder identified by the presence of darker hyperpigmented patches on the face or on other regions of the body that are frequently exposed to the sun, such as, neck, chest, arms, and the back.[1] Although the exact etiology of this condition is still largely unknown, several factors have been identified to play a significant role in the pathophysiology of melasma, including hormonal disturbance, genetic predisposition, exposure to ultraviolet (UV) radiation, and medications.[2] Melasma primarily affects women who are of reproductive age, particularly those of Hispanic, Asian, Middle Eastern, and North African origin.[3] Women with hormonal dysregulation issues, pregnancy, or those on hormonal contraceptives are likely to suffer from an aggravated form of

Address for correspondence
Dr. Sara Ahmed Ali,
Department of Dermatology, College of Medicine,
University of Al-Qadisiyah, Diwaniyah City, Iraq.
Ph: +9647807861053
Email: sara.ahmed@qu.edu.iq

melasma.[4] Melasma is also prevalent among individuals with Fitzpatrick skin types III to V, who often show poor responses to melasma therapies.[1]

The standard therapeutic approaches for melasma include topical medications, chemical peels, and lasers, which frequently produce satisfactory results. However, there is a subset of patients who usually appear with melasma that is resistant to medication.[5] Patients in this category are often diagnosed with the dermal form of melasma, which is characterized by deeper and less defined areas of hyperpigmentation lesions.[6] This is known as refractory melasma, and this condition poses a significant challenge for dermatologists.[5]

A number of various topical treatments have been suggested for the management of refractory melasma, such as the use of tranexamic acid (TA), Alpha-arbutin, as well as number of herbal extracts, which showed the ability to limit melanin formation in the skin layers.[7] Clinical studies show that TA is very effective in reducing skin hyperpigmentation through the antifibrinolytic activity of the drug. This mechanism is known for suppressing the activation of plasminogen/ plasmin system which drastically affect the generation of melanocyte-stimulating hormones leading to downregulation of melanin synthesis in skin cells.[8] Oral administration or intradermal injections of TA was effective in lowering melasma severity index, intensity of melanin pigmentation, and the size of the hyperpigmented patches.[9] TA combination with other depigmenting medications or with skin laser treatments, offered excellent clinical outcomes and improved patients satisfaction in several therapeutic settings.[10]

Lasers are commonly used in the field of dermatology for addressing diverse skin conditions owing to their accuracy and efficacy. Specifically, the fractional CO2 and the QSNY (QSNY) lasers. These types of lasers showed high efficacy in many skin conditions including skin hyperpigmentation that is associated with refractory melasma.[5] The mechanism through which the fractional CO2 lasers function in targeting melasma is through generating high intensity beam of light capable on destroying excessive melanin granules at the affected region of the skin, while preserving the integrity of nearby healthy tissue.[11] This technique presented accurate focusing on the hyperpigmented areas, leading to the lightening of melasma lesions and enhancement of skin texture through collagen remodeling.[12]

QSNY lasers, on the other hand, provide brief bursts of highly concentrated light at a wavelength of 1064 nm, specifically targeting melanin pigments in the dermis and the epidermis.[5] TA has also been used in combination with QSNY lasers to treat melasma and showed promising results decreasing the pigmentation and an improving in skin tone and quality.[6] Nevertheless, studies highlighted the need for additional research on these applications to improve the clinical outcome, examining the long-term efficacy and safety, and addressing different treatment responses among diverse patient populations. Therefore, the aim of the present study is to examine the efficacy of fractional CO2 laser and QSNY laser in combination with TA to treat women with refractory melasma.

Methods

The cross sectional study included 60 women with refractory melasma. Refractory melisma is characterized by facial hyperpigmentation that lasted for at least a year with application of standard topical medications for at least six months of treatment with limited or no improvement. Patients were recruited from outpatient clinic of the department of dermatology at Al-Diwaniyah Teaching Hospital in Diwaniyah City, Iraq, for the period starting from May 2021 to June 2022. Patients were informed about the aims of the study, and those who agreed to take part were provided with formal written consent. The study was approved by the ethical and scientific committee in the College of Medicine at Al-Qadissiyah University (Ref. 62) on April 21, 2021.

Patients' exclusion criteria included pregnancy,

breastfeeding, hormonal dysregulation conditions, hormonal therapy, chemotherapy, autoimmune diseases, blood diseases, thyroid and liver diseases, skin infections (bacterial or viral), and patients with a recent history of facial laser therapy. The current study selected all patients with the same Fitzpatrick skin type and melasma type (skin type IV and dermal melasma). This was performed to ensure uniformity across treatment groups and to reduce any potential variations related to differences in skin types or melasma characteristics.

Patients were randomly assigned to one of the two treatment groups using a computer-generated randomization sequence with a 1:1 allocation ratio, 30 patients per group to either be treated with the fractional CO2 laser or the QSNY laser. Patients from both groups were supplemented with intradermal microinjections of TA. At each laser session, a topical local anesthetic agent (Lidocaine 5%) was applied for 30 minutes to the affected regions of the face and then washed off. Each patient received a total of four laser sessions (one per month) at the following parameters for the fractional CO2 laser. A pulse energy of 22 mJ and a pulse rate of 75/cm^2, utilizing the ECO2 Plus system from Lutronic, USA. The QSNY laser (Picoplus from Lutronic, USA), on the other hand, had a fluence of 0.5 J/cm^2, a frequency of 10 Hz, and 4 passes were made during each session. Immediately following the laser therapy, patients received intradermal microinjections of TA at a concentration of 4 mg/ml (Mesostetic Company, Spain) with a final injection volume of 2 ml. Patients were advised to minimize prolonged and direct sun exposure and to use sunscreens for a minimum of one week following the therapy session.

Modified melasma area and severity index (mMASI) was calculated as described by Aryal *et al*.[13] The baseline melasma severity score was evaluated on the first day of the visit. Treatment assessments with mMSAI scoring were conducted one month after each laser therapy session, specifically at 30, 60, 90, and 120 days. Three independent dermatologists who were blinded to the treatment sessions performed mMASI evaluations. Those blinded raters were provided with digital photographs of patients taken with a Canon EOS R7 camera (Canon-Japan), which has 32.5 Megapixel sensor, and asked to assess the severity score.

Similarly, the patient satisfaction score (PSC) to the outcome of the treatment procedure was assessed by providing the patients with a questionnaire that involved measuring the overall satisfaction with melasma treatment after two months of last laser session. The scores were defined as poor for less than 25% improvement, fair for 25 to 50% improvement, good for 50 to 75% improvement, and excellent for higher than 75% improvement.

Statistical analysis was performed by utilizing SPSS package 28.0 software (IBM SPSS statistics, USA). All continuous variables were assessed for normality using Shapiro-Wilk test and demonstrated a normal distribution. Continuous parameters were expressed as mean values ± standard deviations (SD). Categorical variables were expressed with counts and percentages (%). Independent samples *t*-test was used to compare between continuous variables, whereas Chi-square (χ2) was used to compare between categorical data. The t-test for paired samples was employed to compare between mMASI scores before and after treatment for each therapeutic approach. Statistical significance was determined for $p<.05$.

Results

Sixty women with refractory melasma were included in this study. Demographic data is presented in **Table 1**. The overall mean age was (36.7±9.4) years, with an age range extending from 22 to 55 years. There were no significant differences in the ages of patients between the groups ($P>.05$). There was a with a higher proportion of women below the age of forty years. Investigating the duration of melasma revealed no significant differences between the groups ($P>.05$), with the overall mean duration being (2.7±1.2) years.

Table 1 Summary of patients' demographic data according to the type of laser therapy.

Patient's parameters	*Total*	*Type of laser therapy*		*P-value*
		Fractional CO2	*QSNY*	
Age (years)	36.7±9.4	37.8 ± 8.0	35.6 ± 10.0	.365[†]
Age groups (years)				
Under 30	17 (28.3%)	5 (16.7%)	12 (40.0%)	
31-40	23 (38.3%)	14 (46.7%)	9 (30.0%)	.003[*‡]
41-50	12 (20.0%)	9 (30.0%)	3 (10.0%)	
51 and older	8 (13.3%)	2 (6.7%)	6 (20.0%)	
Sex				
Male	0	0	0	-
Female	60 (100%)	30 (50%)	30 (50%)	
Duration of the condition (years)	2.7±1.2	2.6 ± 1.1	2.7 ± 1.3	.840[†]

[†] T-test for independent samples, [‡] Chi-square test, [*] Significant at P<.05.

Table 2 Treatment responses as measured with mMASI score before and after therapy sessions for fractional CO2 laser and QSNY laser. Lower mMASI scores over time indicate better responses.

Type of laser treatment	*Baseline*	*Post-treatment (days)*			
		30[§]	*60[§]*	*90[§]*	*120[§]*
Fractional CO2 laser involving intradermal TA					
mMASI score (Mean±SD)	14.43 ± 3.5	8.75 ± 3.1	5.25 ± 2.7	4.7 ± 2.9	1.98 ± 1.0
P-value[‡]	-	<0.001*	<0.001*	<0.001*	<0.001*
QSNY laser involving intradermal TA					
mMASI score (Mean ± S.D.)	13.53 ± 4.22	9.3 ± 3.4	5.8 ± 2.9	4.9 ± 2.2	3.1 ± 1.5
P-value[‡]	-	<0.001*	<0.001*	<0.001*	<0.001*

*[‡]T-test for paired samples, [§]Compared to baseline, * Significant at P<.05.*

Treatment responses were quantified using the mMASI score and are summarized in **Table 2**. Patients who received fractional CO2 laser treatment combined with intradermal injections of TA exhibited significant (*P*<.001) improvement in mean mMASI scores compared to the baseline. In addition, patients who were treated with the QSNY laser with intradermal injections of TA also demonstrated significant reduction in mMASI score from baseline, (*P*<.001). No significant adverse effects were identified in either of the treatment groups.

The mean mMASI score after four laser sessions showed significant difference (*P*<.001) between the two treatment approaches **(Table 3)**. The fractional CO2 laser treatment with intradermal injections of TA presented a far better mean mMASI score compared to QSNY laser, being (1.98±1.0) and (3.1±1.5), respectively. This highlights the enhanced effectiveness of the fractional CO2 laser in combination with intradermal injection of TA in improving the melasma condition. However, patients' satisfaction score showed no significant difference between the two treatment groups. The result indicates that the overall satisfaction levels of patients were similar at the end of the follow up duration.

Discussion

The current study showed significant improvement in skin hyperpigmentation among patients with refractory melasma after the use of fractional CO2 laser and QSNY laser in combination with TA intradermal injections. Fractional CO2 laser with TA injections was found to be significantly more effective in reducing the overall melasma severity score in patients, QSNY laser with TA injections is also beneficial. This has been confirmed by assessing mMASI and PSC scores. The findings align with existing reports, highlighting the fact that fractional CO2 laser is very efficient and more effective in addressing refractory melasma.[14] Regarding the mean age of patients, findings were consistent with earlier reports of age range between twenties and late thirties.[5,15]

Table 3 Evaluating degree of melasma improvement according to mMASI and PSC scores after concluding lasers treatments.

Treatment outcomes	*Fractional CO2 laser involving intradermal TA*	*QSNY laser involving intradermal TA*	*P- value*
Degree of improvement of the mMASI (Mean±SD) After four laser sessions and 120 days of the initial assessment. Lower mMASI mean indicates better response.	1.98±1.0	3.1±1.5	0.001*†
PSC (Mean±SD) Two months post the last laser session Higher score indicates higher patient's satisfaction.	2.71±1.7	2.86±0.4	0.123†

*† T-test for independent samples, * Significant at P<0.05.*

Figure 1 A 56-year-old woman suffered for 3.5 years from refractory melasma. The patient received four sessions of fractional CO2 laser involving intradermal TA injections, (A) before, (B) after treatment.

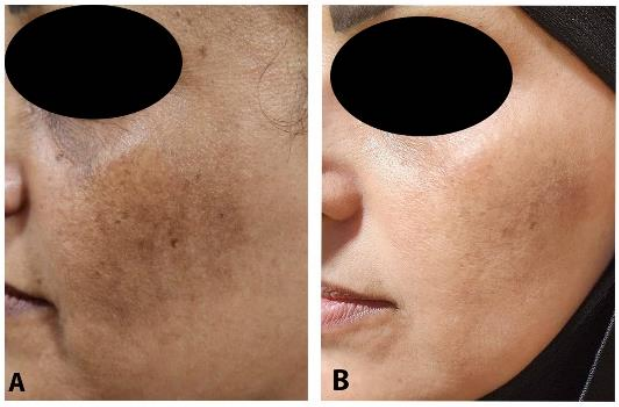

Figure 2 A 43-year-old woman suffered from refractory melasma for 2 years. The patient was treated with four laser sessions of Nd QSNY laser involving intradermal TA, (A) before, (B) after treatment.

The study unveiled high percentage of women were under the age of forty. Bostan and Cakir reported a higher incidence of melasma among women of reproductive age.[3] Similar observations were made by others and indicate that melasma is predominantly affecting women in their mid-to-late thirties of age.[2] This is a vital time frame in women's life which is usually associated with longer hours of sun exposure, pregnancies, administration of hormonal contraceptives, and other hormonal irregularities.[16] In fact, estrogen hormone is found to regulate melanogenesis and transformation of melanocytes into keratinocytes.[4] Irregularities in estrogen levels was found to intensify hyperpigmentation through amplifying the effects of UV radiation on skin cells.[17] The role of hormonal theory may account for melasma, however, the exact nature of this relationship remains incompletely understood.[2] Understanding patients' demographic bias is therefore crucial and essential for developing precise interventions that are required to prevent and manage melasma, particularly for women at reproductive years.

Regarding the duration of melasma, the study showed no significant variations between treatment groups (*P*>.05), with an average duration of 2.7 years. Daroach *et al*. reported melasma durations beyond six years.[18] A strong correlation was found between severity and duration of melasma and the likelihood of developing psychiatric disorders, such as depression, anxiety, and low self-esteem.[19,20] The result highlights the need to include the psychological components of melasma in addition to the clinical treatment.

Regarding laser therapy, findings showed combination of fractional CO2 laser and intradermal TA injections resulted in significant lowering of mMASI score compared to the baseline score (P<.001). The findings are in agreement with

previous studies,[5,10,11,21] and combining TA with fractional CO2 laser can result in better clinical outcomes in comparison to using either treatments individually.[22] This is owing to the fact that fractional CO2 lasers effectively enables TA to reach deep layers of the skin with minor side effects.[23] A study performed by Kamal *et al*. discovered that the use of fractional CO2 lasers with TA can effectively reduce melasma severity and the likelihood of recurrence.[24] Similar findings were also reported by Qu *et al*. who showed that combination application of fractional CO2 laser and TA injections presented significant improvement compared to the fractional CO2 laser alone.[25] Similar results were also reported by Qu *et al*. who found that fractional CO2 laser and a topical TA is safe and effective approach to treat resistant melasma.[25] In addition, this approach was proven to be an effective and viable option for treating people with melasma how are recognized with skin of color.[26]

Regarding the use of QSNY laser and intradermal TA, the study showed significant reduction of mMASI scores (P<.001). Similar results were reported by Hawwam *et al*. who demonstrating that the QSNY laser can be used to reduce skin hyperpigmentation through affect on melanin granules in the deep layers of dermis.[27] Agarwal and Velaskar conducted a study on skin rejuvenation using QSNY laser. They discovered that this approach can effectively treat abnormal skin pigmentation, tone, and texture.[28] Similar results were also reported by Ehsan *et al*. who demonstrated high efficacy of QSNY laser in the treatment of melasma.[29] In contrast, the efficacy of QSNY laser was challenged with a number of side effects, such as recurrence and hypopigmentation.[9] Nevertheless, a study found that effect of QSNY laser can be enhanced with the use of TA as adjuvant.[30]

The current study showed that fractional CO2 laser with TA injections is more effective than QSNY laser with TA injection for refractory melasma. Elmasry *et al*. reported comparable findings and showed that treating melasma with fractional CO2 laser can produce better clinical outcomes that can last.[11] Beyzaee *et al*. reported higher efficacy of using the combination of fractional CO2 laser and TA compared to QSNY laser with TA in treating refractory melasma.[5] Furthermore, the investigated PSC score by the current analysis did not present a significant difference between the two treatment approaches according to patients' satisfaction. Both approaches were equally effective in addressing melasma.

There are several limitations to the current analysis. A larger sample size would provide better presentation of the melasma prevalence among women and would also reduce any sampling errors that may arise unintentionally. The inclusion of only female participants was done on purpose to minimize hormonal confounding effects on treatment responses, that might again limit the generalizability of the findings to male patients. In addition, a longer patient follow-up period could provide better evaluation for any potential side effects and recurrence that may arise after treatment.

Conclusion

The use of the fractional CO2 laser and QSNY laser in combination with intradermal TA injections provided effective and efficient approaches in addressing refractory melasma among affected women. The observed skin improvement following CO2 and QSNY lasers with intradermal TA highlights the potential application of these treatment approaches to treat other skin pigmentation conditions. Further investigations are required in these regards, specifically for examining the long-term results, comparative treatment effectiveness, and patient satisfaction.

Declaration of patient consent Author certify that all appropriate patient consent had been taken.

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Conflict of interest No conflict of interest.

Author's contribution

SAA: Substantial contributions to conception and design, acquisition of data, analysis & interpretation of data. drafting the article and revising it critically for important intellectual content. Author has given final approval of the manuscript version to be published and agreed to be accountable for all aspects of the work.

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