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Comparative Efficacy of Fractional CO_2 Laser and Q-Switched Nd:YAG Laser in Combination Therapy with Tranexamic Acid in Refractory Melasma: Results of a Prospective Clinical Trial

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Abstract: Melasma manifests as hyperpigmented macules and patches, usually affecting the face, neck, and rarely upper limbs. This study evaluated comparative efficacy of a fractional CO_2 laser with a Q-Switched Nd:YAG laser in combination therapy with tranexamic acid in refractory melasma. A total of 30 patients with refractory melasma were included in this study. The fractional CO_2 laser (power: 30 w, pulse energy: 30 mJ, tip type: 300, pulse rate: 100/cm^2) was used on one side of the patients' face and three passes of the Q-Switched Nd:YAG (QSNY) laser (Wavelength: 1064 nm, pulse energy: 750 mJ, fluence: 1.50 J/cm^2, spot size: 4 mm × 4 mm, hand piece: fractional) were used on the opposite side of the same patient's face for six sessions. During the course of laser therapy, all patients received oral tranexamic acid 250 mg twice daily. Melasma area and severity index (MASI) score and physician's satisfaction and patient's satisfaction were analyzed. Thirty patients (mean age 39.97) were included. Patient global assessment (PtGA) in the fractional CO_2 laser group was significantly better than the Q-Switched Nd:YAG laser group at 4th, 8th and 12th weeks (p-value < 0.001). According to PtGA, the improvement was significant in both groups over time. Physician global assessment (PGA) at the 8th and 12th weeks, and physician satisfaction (PS) at the 8th week, in the fractional CO_2 laser group was significantly better than the Q-Switched Nd:YAG laser group (p-value < 0.05). The PGA in both groups significantly reduced over time. The MASI score significantly decreased in both groups over time. The MASI score in the fractional CO_2 laser group decreased more than the Q-Switched Nd:YAG laser group over time ($p < 0.001$). The most common side effects reported were erythema and discomfort, which subsided in less than 24 h. A fractional CO_2 laser with oral tranexamic acid is an effective and well tolerated therapeutic method for the treatment of patients with refractory melasma.

Keywords: comparative efficacy; melasma; fractional CO_2 laser; tranexamic acid

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1. Introduction

Melasma, an acquired prevalent pigmentary disorder, manifests as hyperpigmented macules and patches. This manifestation most commonly affects the face and rarely other areas such as the neck and upper limbs. The prevalence of melasma is higher in young women with IV–V Fitzpatrick skin type [1,2]. A positive family history, UV light exposure and hormonal factors (as evidenced by flare during pregnancy and use of oral contraceptive pills) are the most common risk factors associated with melasma [3–7]. Treatment modalities for melasma can be broadly divided into medical (including oral and

topical), and cosmetic (laser therapy, phototherapy and chemical peels) therapy. Topical hydroquinone (HQ) and the combination of hydroquinone, tretinoin, and fluocinolone acetonide (triple therapy) are still considered as the gold standard treatment. Tranexamic acid, an anti-fibrinolytic drug, is found to be effective, both in its oral as well as topical form. Various lasers and light sources have been proposed in the treatment of melasma [8]. Q-switched Nd:YAG laser (QSNY), fractional laser and intense pulse light (IPL) are energy-based treatment modalities [9–16]. Fractional carbon dioxide (CO_2) laser produces dermal microthermal zones and is used in the treatment of scar but also superficial pigmentations such as melasma [17].

Despite available options, treatment of melasma can be challenging. We did not find any study comparing the efficacy of two laser modalities in combination with medications. We conducted a comparative study to evaluate the efficacy and safety of a fractional CO_2 laser with a Q-Switched Nd:YAG laser in combination with tranexamic acid in refractory melasma.

2. Materials and Methods

In this study, thirty patients with refractory melasma, i.e., those treated with at least two standard medications, for a minimum duration of three months, that had less than 25% improvement (evaluated by modified MASI score), were enrolled. Patients with autoimmune diseases, hepatitis, coagulopathies, and thyroid disorders, and those treated with phenytoin, tranexamic acid (over the past one month), retinoid drugs (over the past three weeks), topical medications to improve skin pigmentations (over the past one month), hormone therapy (such as OCP), anticoagulant agents, or laser therapy to treat melasma (over the past 6 months), and those with a history of allergy to tranexamic acid were excluded. Pregnant women or breastfeeding mothers and patients expressing dissatisfaction with the mentioned treatment techniques were also not included.

The fractional CO_2 laser (power: 30 w, pulse energy: 30 mJ, tip type: 300, pulse rate: 100/cm^2, ECO_2 Device, LUTRONIC company, Gyeonggi-do, Korea) was applied to one side of the face and three passes of the Q-Switched Nd:YAG Laser (Wavelength: 1064 nm, pulse energy: 750 mJ, fluence: 1.50 J/cm^2, spot size: 4 mm $\times$ 4 mm, hand piece: fractional, JEISYS company, Seoul, Korea) were applied to the other side. Throughout the 12-week course, all patients received 250 mg oral tranexamic acid twice daily. A total of six sessions of laser therapy was given, two weeks apart. In the initial assessment (screening), before the start of the treatment process, the patient's facial hyperpigmented lesions were photographed by a digital camera (Canon EOS, Tokyo, Japan). Then, in the follow-up sessions (4th, 8th and 12th weeks), the extent and amount of pigmentation was compared to the first session and the mentioned indexes were re-evaluated. After treatment, patients were followed up for another 12 weeks. Treatment efficacy was evaluated using the patient's global assessment (PtGA) and the physician's global assessment (PGA) scales. Objective evaluation was based on improving the intensity of skin pigmentation by viewing serial images taken from hyperpigmented lesions (photo-documented). Adverse events were recorded. The TSQM (treatment satisfaction questionnaire for medication) was used to assess treatment satisfaction. Quality of life was assessed with the dermatology life quality index (DLQI). The study was approved by the Institutional Ethics Committee. Written consent was obtained from all patients.

Statistical analysis: Continuous variables are presented as mean and standard deviation (SD). Categorical data are presented as frequency and percentages. Categorical data were compared using Chi-Square test and Fisher's exact test as appropriate. Continuous variables were compared using two tailed paired *t*-test and independent *t*-tests. Patient global assessment and patient satisfaction changes were assessed over time. A p value of less than 0.05 was considered as statistically significant.

3. Results

A total of 30 patients with a mean ± SD age of 39.97 ± 7.36 years (minimum age 28 years and maximum age 66 years) were included in this study. The mean ± SD duration of disease was 6.55 ± 8.73 years. Patient global assessment (PtGA) in the fractional CO_2 laser group was significantly better than the Q-Switched Nd:YAG laser group at the 4th, 8th and 12th weeks ($p < 0.001$) (Table 1).

Table 1. Mean and standard deviation of PtGA and PtS over time.

	Q-Switched Nd:YAG Laser		Fractional CO_2 Laser		
	Mean	**Standard Deviation**	**Mean**	**Standard Deviation**	***p*-Value**
PtGA-Baseline	3.70	0.70	3.63	0.93	0.755
PtGA-4	3.73	0.78	2.87	0.68	0.000
PtGA-8	3.13	0.82	2.37	0.61	0.000
PtGA-12	2.47	0.68	1.93	0.78	0.007
p-value	0.000		0.000		
PtS-4	3.83	0.91	3.67	0.76	0.445
PtS-8	3.13	0.86	2.80	0.76	0.117
PtS-12	2.53	1.04	2.07	0.91	0.069
p-value	0.000		0.000		

PtGA decreased significantly in both groups over time. There was an interaction between time and the groups, meaning that PtGA in the fractional CO_2 laser group decreased more than the Q-Switched Nd:YAG laser group over time ($p < 0.001$). Physician global assessment (PGA) at the 8th and 12th weeks, and physician satisfaction (PS) at the 8th week, in the fractional CO_2 laser group was significantly better than the Q-Switched Nd:YAG laser group ($p < 0.05$) (Table 2).

Table 2. Mean and standard deviation of PGA and PS in both groups over time.

	Q-Switched Nd:YAG Laser		Fractional CO_2 Laser		
	Mean	**Standard Deviation**	**Mean**	**Standard Deviation**	***p*-Value**
PGA-B	3.53	0.94	3.47	0.90	0.780
PGA-4	3.30	0.75	2.90	0.92	0.071
PGA-8	2.73	0.64	2.33	0.66	0.021
PGA-12	2.43	0.73	2.00	0.74	0.026
p-value	0.000		0.000		
PS-4	3.83	0.53	3.60	0.62	0.123
PS-8	3.23	0.63	2.80	0.76	0.019
PS-12	2.50	0.78	2.17	1.09	0.177
p-value	0.000		0.000		

The PGA in both groups significantly reduced over time. There was no significant difference in the rate of PGA reduction between groups over time ($p > 0.05$). The MASI score in the fractional CO_2 laser group was significantly lower compared to the Q-Switched Nd:YAG laser group at the 8th week ($p < 0.05$). The MASI score significantly decreased in both groups over time. The MASI score in the fractional CO_2 laser group decreased more than the Q-Switched Nd:YAG laser group over time ($p < 0.001$) (Table 3).

Table 3. Mean and standard deviation of the MASI score in both groups over time.

	Q-Switched Nd:YAG Laser		Fractional CO_2 Laser		
	Mean	**Standard Deviation**	**Mean**	**Standard Deviation**	***p*-Value**
MASI-B	5.14	2.76	4.89	2.05	0.702
MASI-4	4.46	2.69	3.45	2.36	0.129
MASI-8	4.25	2.49	2.12	1.76	0.000
MASI-12	2.52	2.45	1.84	1.91	0.237
p-value	0.000		0.000		

The most common side effects reported were erythema and discomfort, which subsided in less than 24 h. There was no significant difference in the frequency and type of adverse events between groups ($p > 0.05$). The pictures of patients before and after treatment in both groups are shown in Figures 1 and 2.

Figure 1. Response before and after treatment with the fractional CO_2 laser.

Figure 2. Response before and after the Q-Switched Nd:YAG (QSNY) laser.

4. Discussion

Melasma manifests as symmetric mottled hyperpigmented macules and patches. It is one of the most common conditions with which a patient presents to the dermatologist [1,2]. Q-switched Nd:YAG lasers (QSNY), fractional lasers and intense pulse light (IPL) are energy-based treatment modalities used in the treatment of hyperpigmented skin lesions [9–11]. Fractional CO_2 laser facilitates the penetration of tranexamic acid into tissues; therefore, a lower dosage of tranexamic acid is required to achieve the desirable therapy goal [3]. Tranexamic acid is an analogue of the amino acid lysine, which inhibits plasmin activity by binding to plasminogen in keratinocytes. In addition, through mechanisms such as decreasing tyrosinase activity in melanocytes, increasing vascular endothelial growth factor (VEGF) and alpha-melanocyte stimulating hormone (α-MSH), it can be used as a treatment modality for melasma patients [15,16]. In the past decade, the safety and efficacy of Q-switched Nd:YAG lasers have been widely demonstrated in many different conditions such as melasma, tattoo removal, and other dermatological conditions [18,19].

In our study, the fractional CO_2 laser was found to be superior to the QSNY laser. In addition, PtGA and Pts scores decreased significantly over time, indicating that patient satisfaction and efficacy of the laser therapy in primary sessions improved. Jalali et al. reported a significantly lower mMASI score in the fractional CO_2 laser group than the QSNY group. The reduction in MASI score in the fractional CO_2 laser group was significantly more than the Q-Switched Nd:YAG laser group over time [4]. Our results are concordant with this study. Kwon et al. studied the efficacy of a QSNY laser versus combination therapy of a QSNY laser with fractional microneedling radiofrequency in the treatment of melasma. They reported a significant reduction of PtGA in the combination therapy compared to the monotherapy group. However, there was no significant difference in patient satisfaction between the two groups [5]. The results were concordant with our study, in terms of the efficacy of the Q-switched Nd:YAG laser. Tawfic et al. studied the efficacy of a fractional CO_2 laser versus combination therapy with a fractional CO_2 laser and topical tranexamic acid. According to MASI score, melanin index, erythema index and PS score, improvement of melasma lesions in the combination therapy group was better than the monotherapy group, but without a statistically significant difference [20]. The results were concordant with our study in terms of the efficacy of a fractional CO_2 laser and tranexamic acid. Kee et al. studied the efficacy of a 1064-nm Q-switched Nd:YAG laser (n = 23 patients with melasma). In this study, patients underwent ten sessions and were followed-up for three months. The therapy was effective and the patient satisfaction score also improved significantly [21]. The efficacy results of the Q-switched Nd:YAG laser were concordant with our study. Arielle et al. studied the efficacy of a low fluence Q-switched Nd:YAG laser with microdermabrasion. A total of 27 female patients were included and followed-up for 12 weeks after treatment. At the end, all patients had complete recovery. They found that the combination therapy with the Nd:YAG laser and microdermabrasion was an effective non-invasive method for treating melasma [22]. The results were concordant with our study in terms of the efficacy of the Q-switched Nd:YAG laser. Cho et al. studied the efficacy of a 1064-nm Q-switched Nd:YAG laser in 25 female patients with melasma. The patients were followed-up for eight weeks. The MASI score and patient satisfaction score significantly improved after treatment [23]. Sim et al. studied the efficacy of a 1064-nm Q-switched Nd:YAG laser to treat 50 Asian patients with melasma. Objective assessment, and patient satisfaction score significantly improved [24]. The results were concordant with our study in terms of the efficacy of the Q-switched Nd:YAG laser. Sanaz et al. studied the efficacy of hydroquinone versus combination therapy of hydroquinone with a fractional CO_2 laser. Forty patients with melasma entered the study and were treated for 12 weeks. In the end, the MASI score in the combination therapy group was significantly better ($p < 0.001$) [25], and the results were concordant with our study in terms of the efficacy of the fractional CO_2 laser. Suhattaya and colleagues studied the efficacy of a Q-Switched Alexandrite laser versus combination therapy of a Q-Switched Alexandrite laser with an Ultrapulse CO_2 laser with follow up of six months. The MASI score and melanin index

score in the combination therapy group were significantly better ($p < 0.05$) [10]. The results were concordant with our study in terms of the efficacy of the fractional CO_2 laser. Overall, the most common side effects were erythema and discomfort, which subsided in less than 24 h, without a significant difference between the two groups.

The limited number of patients and short term follow up are important limitations of our study. Longer studies with larger sample sizes are required to confirm observations in our study. Long-term monitoring to evaluate the recurrence rate is recommended in future studies. Moreover, as we studied the efficacy in only one skin type, extrapolation of these results to other skin types need to be done with caution.

5. Conclusions

The results of our study show that a fractional CO_2 laser with oral tranexamic acid is an effective and well tolerated therapeutic method for the treatment of patients with refractory melasma. Long term studies in people with different skin types are required to evaluate the efficacy and recurrence rate with this therapy.

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