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Original Article

Therapeutic efficacy and safety of Fractional Carbon dioxide Laser versus Q-Switched Nd:YAG 1064nm Laser in the treatment of Melasma: A comparative interventional study

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Abstract

Objective To compare the efficacy and safety profile of fractional CO_2 laser versus Q-switched Nd:YAG 1,064 nm laser while treating various subtypes of melasma.

Methods Eighty six patients of 18 years to 40 years of either gender, suffering from Melasma involving superficial epidermis, deep dermal melanosis or with coexisting both subtypes not taking any treatment for last 6 months were included. Patients with cutaneous and systemic co-morbidities were excluded. Pre-treatment MASI was calculated. Patients were randomized into two Groups, Group A and Group B with 43 patients each, with resistant melasma underwent Fractional Carbondioxide Laser and Q-Switched Nd:YAG 1064 nm Laser respectively. Treatment was done every four weeks for five consecutive sessions and response was assessed at one month follow up. Pictorial evidence of facial cutaneous melanosis was made into account using a DSLR camera at their first presentation to keep a record of primary lesion and prior to undergoing procedure (at four weeks interval) for comparison.

Results Patients undergoing both the laser treatments mean age of 30.2±8.1 years. Fitzpatrick skin type V was most frequent followed by type IV. Majority (50.0%) had centrofacial melasma followed by malar (37.2%), mixed (9.3%) and mandibular (3.5%). It was epidermal in 52 (60.5%) patients while dermal and mixed in 14 (16.3%) and 20 (23.3%) patients respectively. A comparison between groups (A and B) was made on the basis of mean MASI score at presentation (16.4±12.9 vs. 16.8±18.6; p-value=0.921). Mean MASI score reduced significantly in both groups after 1 month of treatment; Group A (16.4±12.9 to 6.4±8.9; p-value<0.001) and Group B (16.8±18.6 to 12.3±15.2; p-value<0.001). The follow-up mean MASI score was markedly low in patients undergoing fractional CO_2 laser in comparison with Q-switched Nd:YAG 1064 nm laser (6.4±8.9 vs. 12.3±15.2; p-value=0.030). Taking ≥60% reduction in baseline MASI score as efficacy, efficacy was significantly higher in cases with fractional CO2 laser treatment than Q-Switched Nd:YAG 1064 nm laser (86.0% vs.46.5%; p-value<0.001).

Conclusion Fractional CO_2 laser is more efficacious in treating melasma.

Key words
Melasma, MASI, fractional CO_2 laser, Q-Switched ND:YAG 1064nm laser.

Introduction

Melasma, a term referred as Chloasma, is a very commonly acquired hyperpigmentary condition that presents with irregularly shaped brown or greyish hypermelanosis at sun exposed skin particularly face.[1] It manifests mainly in Latin and Asian women aged 30 to 55 years with

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lesions mostly occurring on sites like forehead, zygomatic process, upper lip, chin and temple.[2] Pregnancy, use of oral contraceptive pills and exposure to ultra-violet radiations have been linked to the appearance of melasma.[1,2]

Clinically, melasma is classified on the basis of site of distribution as malar, centrofacial and mandibular while histopathologically three patterns are recognized: epidermal, dermal and mixed types. Epidermal and dermal melasma are clinically differentiated by Wood's lamp.[2]

Pathogenesis involves disruption in any of the following mechanisms: biogenesis of melanosome; processing of melanogenic proteins into melanosomes followed by intercellular transport into neighbouring keratinocytic cell layer.[2]

Multimodal topical, systemic and physical modalities are utilized in treating melasma as topical applications of skin lightening and chemical peeling agents, microdermabrasion, and various light and laser adjuncts including IPL- intense pulsed light, Q-Switched lasers (neodymium doped yttrium aluminium garnet, ablative and non-ablative fractional resurfacing carbon dioxide and pico lasers are proven to be effective in treating widespread longstanding epidermal and resistant dermal melanosis.[2]

CO_2 laser (wavelength 10,600nm) is a new modality in the treatment options of melasma.[6] Fractional thermolysis by CO_2 laser results in extrusion of microepidermal necrotic debris (MEND).[7] The MENDs act as "melanin shuttles". They package excess melanin and help in its elimination through stratum corneum. Besides this, fractional CO_2 laser causes thermal damage to the existing basal cell layer leading to the formation of new basal cell layer with lesser melanin.[7] Fractional CO_2 laser has shown promising results with no detrimental effect on the epidermis as it uses vertical channels of coagulative tissue in micro-thermal zones (MTZ) producing photothermolysis yet with least residual post inflammatory hyperpigmentation.[6]

Q-Switched ND:YAG 1064 nm laser produces high local temperature gradient between melanosomes and their surrounding structures causing melanosomes to fracture.[8] High pressure acoustic waves from this interaction lead to melanocyte death, therefore, it is more safer and known for significant effectivity when it comes to treating various forms of melasma.[3-5]

In a study conducted in South Korea, efficacy of Q-Switched Nd:YAG 1064 nm in treating melasma was evaluated.[4] Results showed clinical improvement in terms of recognizable decrease in MASI score as well as patient satisfaction.[4]

A study was conducted in Tehran between 2011-2013 to compare safe use and effectivity of low power fractional CO_2 laser versus low fluence Q-Switched Nd:YAG 1064 nm laser while treating facial hyperpigmentation.[6] Mean Melanin Index (MI) and MASI scores at presentation and two months post procedure follow-up were compared and revealed the treated side of the face showed relatively marked improvement with Fractional carbondioxide Laser with significant reduction in MI and MASI sore than Q-Switched ND:YAG 1064 nm Laser.[6]

We aimed to carry out a study in order to compare the effectiveness and safety of fractional CO_2 laser and Q-Switched Nd:YAG 1064 nm laser in treating various forms of melasma in our community. Limited studies are available internationally on fairer skin types which are not applicable on our skin types. That's why there is a need to establish the

efficacy of CO_2 laser and Q-Switched Nd:YAG 1064nm laser in Fitzpatrick darker Asian skin IV, V population.

Materials and methods

Study design Observer blind randomized clinical trial/ comparative interventional study.

Setting Study has been conducted in the outpatient clinic of the Dermatology Department Unit-II, King Edward Medical University, Mayo Hospital, Lahore.

Duration of study Study was conducted for a period of six months from July 2021 to December 2021.

Sample size Sample size of 86 patients was calculated. 43 patients have been treated with-fractional CO_2 laser and the remaining 43 with Q-Switched ND:YAG 1064 nm laser. Sample size was calculated by using 90% Power of the test, 1% Level of significance and by taking expected percentage of reduction in MASI score from base line till last follow up visit with CO_2 Laser and Q-Switched Nd:YAG 1,064 nm as 49.84% and 85.41% respectively.[6]

$$n = \frac{\left\{ z_{1-\alpha}\sqrt{2\bar{P}(1-\bar{P})} + z_{1-\beta}\sqrt{P_1(1-P_1)+P_2(1-P_2)} \right\}^2}{\left(P_1 - P_2\right)^2}$$

Where $\mathbf{P_{1=}}$ Population proportion I = 49.84%, $\mathbf{P_{2=}}$ Population proportion II = 85.41%, $\mathbf{z_{1-\alpha=}}$ confidence level = 99%, $\mathbf{z_{1-\beta=}}$ Power of test = 90%

Sampling technique Non-probability consecutive sampling.

Sample selection

Inclusion Criteria Male and Female patients having Epidermal, dermal or mixed type of melasma according to Wood's lamp examination done by the researcher.

Exclusion Criteria

1. Breast feeding as ascertained by history.
2. Use of chemical peels, topical skin lightening agents, laser or light based therapy for hyperpigmented cutaneous condition in the past 3 months determined by history and available record.
3. Prevalent or contagious infectious dermatosis e.g. herpes at the time of presentation.
4. History of Photosensitivity, rosacea, photocontact dermatitis etc. on the basis of history or any available prescription or record.
5. Documentation of keloidal scar formation.
6. Patients taking retinoids, oral contraceptive pills and other drugs causing hyperpigmentation such as minocycline etc. determined by history or any available record.
7. Deranged LFT's and RFT's.

Data collection procedure

Data was collected using a pre-designed proforma. Screening was on first visit. History was taken and clinical examination had been done. Investigations such as Hb, LFT's and RFT's was recorded. Patients included in the study were made to provide written and verbal consent on next visit. Clinical pattern of melasma was noted after Wood's lamp examination. Randomization into two groups was done by random number table generated by SPSS. 43 patients assigned Group A underwent fractional CO_2 laser. 5% lignocaine ointment was applied on face 30 minutes before treatment. Face cleansed, protective goggles were worn by the patient and the doctor, and laser treatment with following parameters were carried out. Spot size 11x11 mm, point energy of 15-20mj, pulse duration upto 3ms, interval 1ms, distance 0.8mm, and fractional scan mode.

Patients were advised to apply sunscreen and moisturizer after treatment. Group B patients, after cleansing of face had Q-Switched Nd:YAG 1064 nm laser treatment with following set of considerations: Pulse duration: 10ns, Frequency: 4-6Hz, Spot size: 3mm. After treatment, patients were provided with a sunscreen (SPF30+) and advised for compliance over two hourly application on the entire face and avoidance of direct ultraviolet exposure during the course of study. Patients were enrolled for five treatment sittings over a four weekly session or till the clearance of melasma whichever achieved first.

Response to treatment had been assessed by MASI score by two blinded qualified dermatologists at one month follow up visit and inter-observer agreement was calculated. Patients had been told about the suspected adverse reactions of Q-Switched Nd:YAG 1064 nm laser treatment: Facial erythema and minimal temporary edema and adversative effects of the fractional CO_2 laser, limited mainly to slight erythematous skin response at times accompanied with burning, followed by transient facial edema and exfoliation, and these were noted on each visit. Follow up had been scheduled one month following completion of successive treatments.

Clinical improvement was graded in accordance with MASI score.[11]

Assessment criteria Assessment of patient was clinical and done by calculating MASI score that quantifies the severity index of presenting cutaneous hypermelanosis [10] on each follow-up.

Data analysis procedure Collected information was transferred to Statistical Package for Social Sciences (SPSS) version 20. Output was presented in the form of graphs and tables for categorical variables. Qualitative variables were gender, type of melasma, marital status and occupation while age, LFTs and MASI score were taken as quantitative variables. Quantitative variables were presented as mean±SD. Qualitative variables were presented as frequency and percentages. Chi square test was used to see the association between qualitative variables. A p value of ≤0.05 was taken as significant.

Results

Patients had mean age 30.2±8.1 years. Majority (91.90%) belonged to 18-39 years of age, while the rest of 8.10% patients aged between 40-60 years. Females were predominant, however male to female ratio was 1:6.2. Fitzpatrick type V was the most frequent skin phototypes and was observed in 59 (68.6%) patients followed by Fitzpatrick type IV (n=27, 31.4%). Majority (50.0%) of the patients had centrofacial melasma followed by malar (37.2%), mixed (9.3%) and mandibular (3.5%) distribution. It was epidermal in 52 (60.5%) patients while dermal and both epidermal and dermal involvement was seen in 14 (16.3%) and 20 (23.3%) patients respectively on wood's lamp examination. Majority (88.40%) of these patients were married.

Both categorically divided grouped patients were compared in standings of mean age (30.1±7.3 vs. 30.3±9.0 years; p-value=0.906) and varied age (p-value= 0.693), gender (p-value=0.534), skin type (p-value=0.816), pattern (p-value=0.405) and type (p-value=0.492) of melasma and marital status (p-value=1.000) as shown in **Figures 1 to 3**.

Mean MASI score at presentation was comparable in both the groups (16.4±12.9 vs. 16.8±18.6; p-value=0.921). Mean MASI score reduced significantly in both the groups after 1 month of treatment; Group-A (16.4±12.9 to 6.4±8.9; p-value<0.001) and Group-B

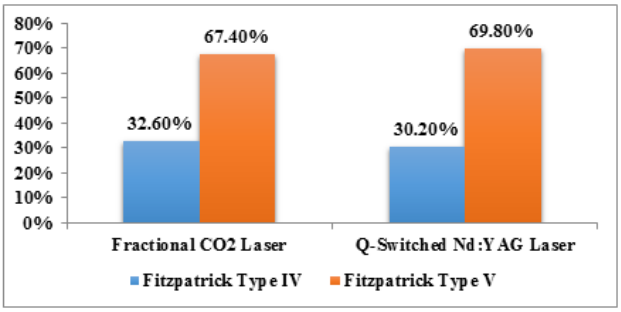

Figure 1 Comparison of various skin types distribution between study groups.
(*Chi-square test, observed difference was statistically insignificant; p=0.816)*

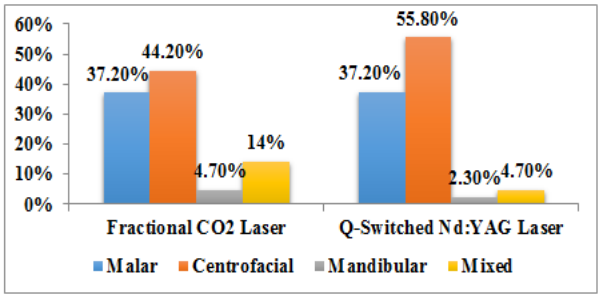

Figure 2 Comparison of various patterns of involvement between study groups.
(Chi-square test, observed difference was statistically insignificant; p=0.405)

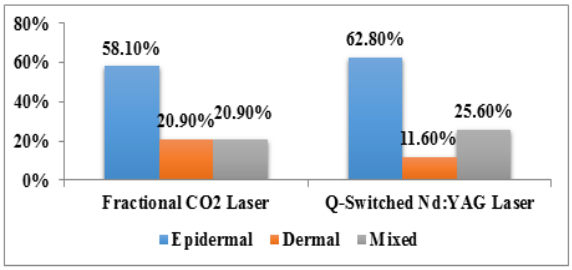

Figure 3 Comparison of findings on wood lamp examination between study groups.
(Chi-square test, observed difference was statistically insignificant; p=0.49)

(16.8±18.6 to 12.3±15.2; p-value<0.001). The follow-up mean MASI score was considerably low with fractional CO_2 laser treated individuals than the ones who underwent Q-Switched ND:YAG 1064 nm laser (6.4±8.9 vs. 12.3±15.2; p-value=0.030) as shown in **Table 1**. 37.2% patients had excellent (≥90% reduction in mean MASI score) while 29.2% patients had good outcome (60-89% reduction in mean MASI score). Satisfactory (30-59% decrease in mean

Table 1 Comparison of mean MASI score at various intervals.

Time Stamp	*Mean MASI Score*		*P-Value~*
	Fractional CO_2 Laser	*Q-Switched Nd:YAG Laser*	
At baseline	16.4±12.9	16.8±18.6	0.921
After treatment	6.4±8.9	12.3±15.2	0.030*
P-Value$	<0.001*	<0.001*	

$: Paired sample t-test comparing change in MASI score from baseline, ~ : Independent sample t-test comparing MASI score between Group, * observed difference was statistically significant

MASI score) while poor (<30% decline in mean MASI score) outcome had been stated in 24.40% and 9.30% patients respectively. The patients receiving fractional CO_2 laser treatment had a higher ratio of excellent outcome as shown in **Figure 4**. Taking ≥60% reduction in the baseline MASI score as efficacy, it was evident with fractional CO_2 laser treatment as compared to Q-switched Nd:YAG 1064 nm laser (86.0% vs. 46.5%; p-value<0.001) as shown in **Figure 5, 6**. In the present study, mild side effects like erythema and edema were observed in all patients regardless of study group as these side effects are common to laser therapy and were easily managed conservatively. None of our patients developed serious side effects for which treatment had to be withheld.

Discussion

Melasma is hypermelanosis predilected on facial skin yet can involve areas of neck and trunk rendered by prolonged ultraviolet exposure.[12] Various etiopathological factors that tend to contribute include genetic predisposition, direct photo damage due to UVAs and UVBs, hormonal influences in a pregnant female and several vascular factors.[12,13] Regardless of vast availability of various treatment modalities including adjunct therapies, studies reveal a very less proportion of patients worldwide who

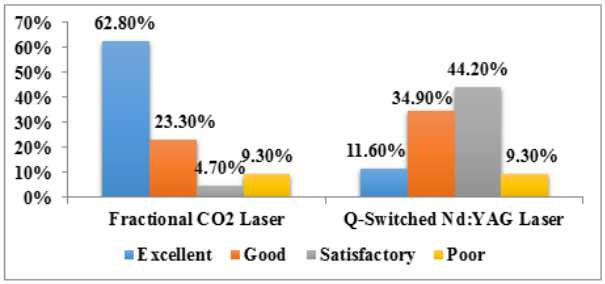

Figure 4 Comparison of various grades of outcome between study groups.
(Chi-square test, observed difference was statistically significant; p<0.0001)

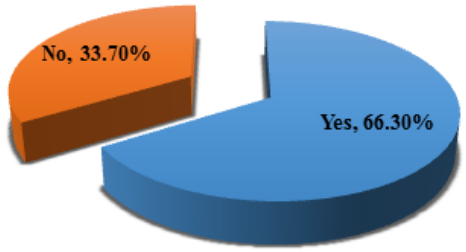

Figure 5 Frequency of efficacy in the study sample.

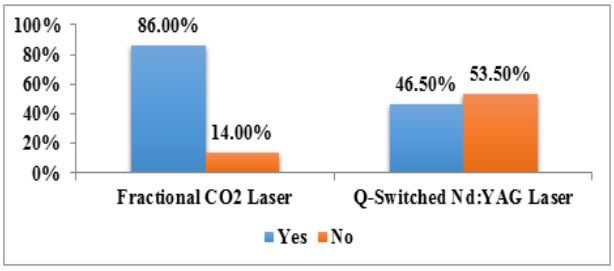

Figure 6 Comparison of efficacy between study groups.
(Chi-square test, observed difference was statistically significant; p<0.0001)

achieve an absolute remission or complete facial pigment regression. Moreover, the propensity of relapses is significant in melanosis involving dermis and rebound hyperpigmentation a drastic adverse reaction of combined topical regimens including tretinin, hydroquinone and steroids reportedly.[12,15]

CO^2 laser (wavelength 10,600nm) is a new modality in the treatment options of melasma.[6] Fractional thermolysis by CO_2 laser results in extrusion of microepidermal necrotic debris (MEND). The MENDs act as "melanin shuttles". They package excess melanin and help in its elimination through stratum corneum. Besides this, fractional CO_2 laser causes thermal damage to the existing basal cell layer leading to the formation of new basal cell layer with lesser melanin[5]. Fractional CO_2 laser has shown promising results with no detrimental effect on the epidermis as it uses vertical channels of coagulative tissue producing photothermolysis yet with least residual post inflammatory hyperpigmentation.[6,7]

Q-switched Nd:YAG 1,064 nm laser produces high local temperature gradient between melanosomes and their surrounding structures causing melanosomes to fracture.[7] High pressure acoustic waves from this interaction lead to melanocyte death, therefore, it is found to be safer and efficacious in the treatment of melasma.[7-9]

Major purpose revolved around carrying out the comparative efficacy and determine safer use of fractional CO_2 laser and Q-switched Nd:YAG 1064 nm laser for treating varied forms of melasma in our Asian community.

The patients in our study had mean age of 30.2 ± 8.1 years. A similar mean age of 30.4±5.8 years has been reported by Ejaz *et al*.[16] among patients presenting with melasma at Combined Military Hospital, Karachi. Aman *et al*.[17] (2017) reported similar mean age of 30.4±9.2 years among such patients presenting at Services Institute of Medical Sciences/ Services Hospital, Lahore while Ali *et al*.[14] (2013) reported it to be 29.9±4.2 years among such patients presenting at King Edward Medical University/ Mayo Hospital, Lahore. A similar mean age of 28.8±6.5 years has been reported by Desale *et al*.[18] (2015) among Indian such patients.

We observed pigmented melanosis predominantly in female population, with a male to female ratio of 1:6.2. Ejaz *et al*.[16] reported similar female predominance in local population with male to female ratio of 1:5.8 while Luqman

et al.[19] reported it to be 1:8. A similar female predominance among Indian melasmic patients has been reported by Divya *et al*.[20] (2017) who observed it to be 1:6.3 while Desale *et al*.[18] reported it to be 1:7.3 in 2015. Kakru *et al*.[21] (2017) reported male to female ratio of 1:5.8 in Nepalese patients with melasma. In the present study, melasma was epidermal in 52 (60.5%) patients while dermal and both epidermal and dermal involvement was seen in 14 (16.3%) and 20 (23.3%) patients respectively on wood's lamp examination. Aamir *et al*.[24] (2014) reported similar frequency of epidermal (61.5%), dermal (23.0%) and mixed (15.5%) involvement in patients presenting with melasma at Sheikh Zayed Hospital, Lahore. Another local study reported similar frequency of epidermal (75.0%), dermal (15.0%) and mixed (10.0%) distribution in such patients at Mayo Hospital, Lahore[25]. Kakru *et al*.[21] (2017) reported similar frequency of epidermal (61.1%), dermal (22.2%) and mixed (16.6%) distribution in Nepalese patients with melasma.

We found that the mean MASI score reduced significantly in either of the studied population after 1 month of treatment; fractional CO_2 laser (16.4±12.9 to 6.4±8.9; p-value<0.001) and Q-switched Nd:YAG laser (16.8±18.6 to 12.3±15.2; p-value<0.001). However, follow-up mean MASI score was markedly low in patients who underwent fractional CO_2 laser than Q-switched Nd:YAG 1064 nm laser (6.4±8.9 vs. 12.3±15.2; p-value=0.030). Also, the ratio of efficacy was remarkable in fractional CO_2 laser treated individuals than the ones undergoing Q-Switched Nd:YAG 1064 nm laser (86.0% vs. 46.5%; p-value<0.001). Our results are comparable to those of Jalaly *et al*.[6] (2014) who as well conducted an RCT reported that both treatments; fractional CO_2 laser (16.3±8.7 to 8.1±5.7; p-value<0.001) and Q-switched Nd:YAG laser (15.8±7.4 to 13.8±6.7; p-value<0.001) resulted in significant reduction of mean MASI score 1 month after treatment. They also observed significantly lower mean follow-up MASI score in patients treated with fractional CO_2 laser as compared to Q-switched laser (8.1±5.7 vs. 13.8±6.7; p-value<0.001) in line with the present study. The authors were conclusive of the fact supporting fractional CO_2 laser being highly efficacious when compared to Q-Switched Nd:YAG laser (85.4% vs. 49.8%; p-value<0.05) in treating melasma.

Considering the fact that we conducted the first ever study evaluating comparative therapeutic laser modalities in treating melasma pertinent to Asian population, a limited evidence could be gathered on internationally conducted trials on similar ethnic grounds. Moreover we reported mild side effects like erythema and edema were observed in all patients regardless of study group as these side effects are common to laser therapy and were easily managed conservatively. None of our patients developed serious side effects for which treatment had to be withheld. Thus it can be concluded that fractional CO_2 laser is more effective yet equally safe in comparison with conventional Q-switched Nd:YAG laser which favor its use in future practice.

Conclusion

Fractional Carbondioxide Laser treatment is more effective and safe in mainly epidermal melasma accounting only transient and mild side effects.

Limitation

Limited follow-up of 1 month and relapsing nature of melasma renders a need for long term follow-up to establish the role of fractional CO_2 laser more clearly. Such a study is highly recommended in future research.

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