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BRIEF REPORT

Efficacy and safety of different low fluences of Q-switched Nd:YAG laser in treatment of melasma: a split-face clinical and dermoscopic comparative study

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Introduction

Low fluence Q-switched Nd:YAG laser at fluences of 2.5~4.5 J/cm^2 has gained attention in treatment of melasma [1, 2], as it penetrates deeper and delivers subthreshold energy targeting melanin particles within keratinocytes and dermal melanophages [3]. This led to good results but with occurrence of some adverse events such as mild linear depigmentation [4] or mottled hypopigmentation [5]. Using lower fluences as 0.8 to 1.6 J/cm^2 [6] or less number of passes [7] can avoid complications in melasma laser toning. Melasma can be assessed by dermoscopy, permitting the observation of its pigment and vascular components [8]. However; its use for follow-up of treatment has not been well established.

Aim of work

This study aims at comparing different fluences of Q-switched Nd:YAG (Qs Nd:YAG) laser that can induce an effective response with best safety for melasma patients. Evaluating the role of dermoscopy in assessing the therapeutic response in cases of melasma is a further objective.

Patients and methods

Patients Thirty-eight patients with bilateral melasma were enrolled in the study. Exclusion criteria were patients with known photosensitivity, pregnant females, on hormonal therapy, or using topical depigmenting creams. Each participant provided a written informed consent for inclusion in the study and photography. The study was approved by the Dermatology Research Ethical Committee (Derma REC), and standards of research ethics according to the Declaration of Helsinki were adopted.

Method This is a split-face randomized comparative study.

Q-switched Nd:YAG laser (1064 nm) treatment protocol

Patients applied topical anesthesia cream for 45 min prior to the procedure. Qs Nd:YAG laser 1064 nm (Fotona's QX MAX®) was used with spot size 6 mm at 4.5 Hz on both sides of face at biweekly intervals. According to randomization table, one side of the face was treated by fluence 3 J/cm^2 for 2 passes (identified as side A) and the other side treated by 1.5 J/cm^2 for 4 passes (identified as side B). In-between sessions and at the 1-month follow-up period, patients were instructed to use sunscreens with SPF 50+ regularly. All patients underwent six sessions performed 2 weeks apart (weeks 0, 2, 4, 6, 8, 10) and then follow-up 1 month after the last session (week 14). Patients were photographed using Nikon Coolpix L100 camera.

Patients' Melasma assessment

Prior to start of treatment patients' assessment for both sides was performed, repeated at week 10 and at week 14 by the following:

Simplified melasma severity index (MSI) scoring = (a-$\times p^2$), where a = area of involvement and p = severity of pigmentation [9].

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Colorimetry evaluating melanin index (MI) and erythema index (EI): Using Dermacatch® colorimeter, which gives a numerical figure for the degree of pigmentation as MI and for degree of erythema as EI.

Dermoscopic assessment: Using × 20 magnification images exported from the digital dermoscope Fotofinder Medicam 1000 (Bad Birnbach, Germany) software system, the pigmentary and vascular features were evaluated through the following 6 dermoscopic criteria of melasma [10, 11]:

-Brown pseudo-network (PN): Diffuse light-to-dark brown pseudo-network.

-Granular pigmentation (GP): Multiple brown dots, granules, or globules.

-Reticular network (RN): Fine brown reticular network

-Perifollicular pigmentation (PP): Arcuate or annular brown pigmentation around follicular openings.

-Erythema (E): Presence of background erythema.

-Blood vessels (BV): Presence of elongated or telangiectatic blood vessels.

Dermoscopic features were evaluated as present or not (+ or -), and results were displayed as percentage of patients demonstrating each feature for each side. Patients typically exhibited multiple dermoscopic features in their lesions.

Pain score: After each session, patients were asked to grade the pain on a scale from 0 to 10 using the Mankoski Pain Scale [12].

Safety assessment

Safety of sessions was evaluated at each visit by recording of side effects such as post-inflammatory hyperpigmentation, erythema, or burning sensation.

Statistical analysis Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 25 (IBM Corp., Armonk, NY, USA). Data was summarized using mean, standard deviation in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Mann-Whitney tests. For comparison of serial measurements within each patient, the non-parametric Friedman test and Wilcoxon signed rank test were used. For comparing categorical data, Chi square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than 5. *P* values less than 0.05 were considered as statistically significant.

Results

A total of 38 female patients with melasma were enrolled; 18.4% were Fitzpatrick skin type III, 76.3% skin type IV, and 5.3% skin type V. The mean age of participants was 42.21 (± 8.11) years, and the mean duration of their melasma was 7.25 (± 6.03) years. Four patients did not complete the study (Fig. 1).

A. Melasma severity index Mean MSI score decreased dramatically from 9.24 at week 0 to 5.05 at week 10 for side A ($P = 0.001$) and from 9.51 to 5.16 for side B ($P = 0.001$). This improvement was mostly maintained with slight worsening after 1-month follow-up, which became 5.78 for side A and 5.88 for side B. There are no statistically significant differences regarding MSI scores between the two treatment modalities throughout the study period ($P > 0.05$) (Fig. 2).

B. Colorimetric evaluation of MI and EI For the two sides, mean MI as well as mean EI decreased significantly at week 10 (for both sides $P = 0.001$) denoting a positive response to treatment parameters, with no statistically significant difference between both fluences (Table 1). This means that melasma improved equally well in response to either laser toning parameters.

C. Dermoscopic assessment On both treatment sides, the dermoscopic characteristics showed no statistically significant differences at week 10 and at 1-month follow-up, where *P* value > 0.05 for all features for both treatment fluences. However, the percentage of patients showing granular pigmentation and pseudo-network pigmentation became less with treatment sessions, while the number of lesions displaying arcuate or annular perifollicular pigmentation increased. Blood vessels were not affected by Qs Nd:YAG laser toning. However, erythema shows some decrease only during regular exposure to sessions **(**Fig. 3**).**

D. Pain score A statistically significant difference was found (*P* value < 0.001) between both sides, where 91.2% of patients felt annoying pain enough to be distracting at side A and none complained of this pain at side B.

E. Safety assessment Side A laser treatment induced temporary erythema lasting for few hours to 3 days, whereas side B induced erythema lasting for maximum 1-day post-session.

Discussion

In the current study, the use of Qs Nd:YAG at 1.5 J/cm^2 for 4 passes or 3 J/cm^2 for 2 passes induced a comparable therapeutic response, with no statistical difference in the outcome as assessed by MSI score ($P = 0.424$), MI ($P = 0.635$), and EI ($P = 0.091$). Previously, the use of Qs Nd:YAG at low-energy levels (fluence of 2.5–3.4 J/cm^2) weekly for nine sessions induced a 35.8% improvement in MI from baseline [13].

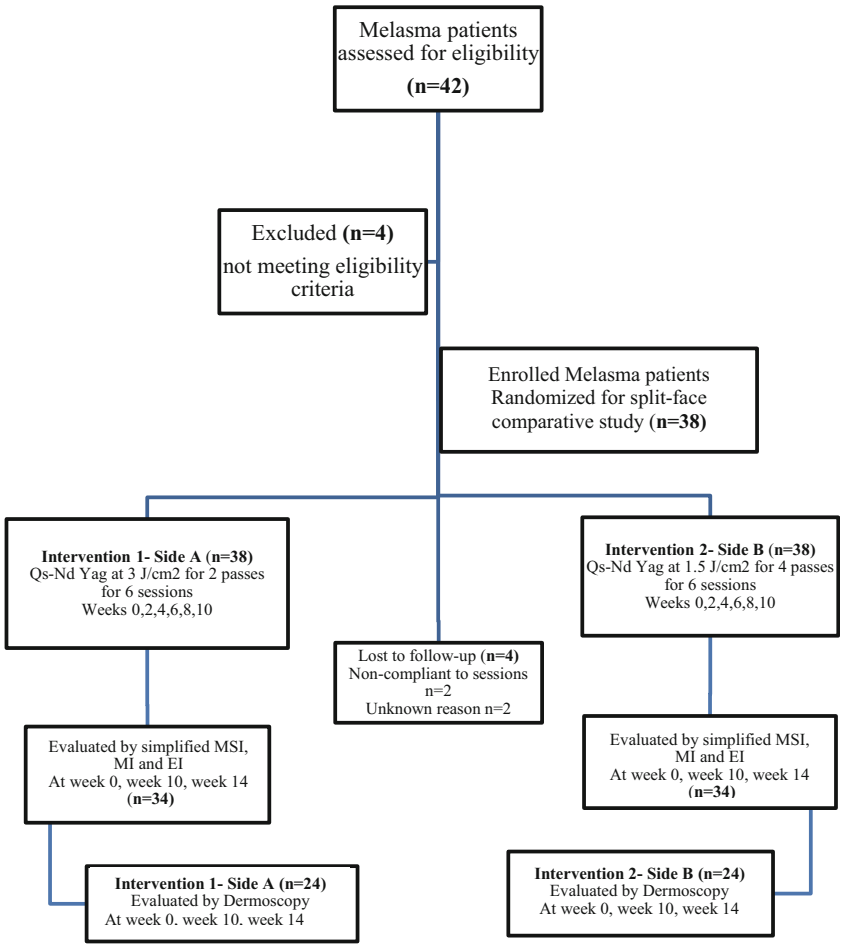

Fig. 1 Workflow diagram of patients

Similarly, in a retrospective study evaluating treatment parameters comparable to side A, a statistically significant improvement (P value < 0.001) in mean mMASI score was observed after 8 biweekly sessions, with patients' satisfaction scored as 50% reduction in their melasma severity [14].

Pain was significantly higher on the side treated with 3 J/cm^2–2 passes (P < 0.001). Although this pain was tolerable and transient as previously reported [4, 6, 15], the 1.5 J/cm^2, 4 passes modality was more acceptable to the patients.

Thus, it is safe to assume that using conservative treatment approaches as lowering the fluence and adjusting sessions' intervals can help optimize the therapeutic outcome and avoid complications in melasma laser toning.

In this study, as well as in all previous studies, the melasma lesions show improvement of pigmentation in response to Qs Nd:YAG but no clearance. This can be explained by the fact that Qs Nd:Yag Laser toning induces decrease in melanin particle surface area and decrease number of MART-1 positive cells in the skin with dramatic decrease in size of melanocytes but remain present [5].

On follow-up after 1 month without any treatment with supposed application of proper sun protection, mild worsening of their melasma was observed. Some patients did not apply sun block creams diligently; thus, with stoppage of any treatment, melasma started to recur. This has been previously reported where 3 months after sessions' stoppage recurrence of melasma has been documented to occur [1, 2]. Hence, laser toning sessions should be administered to patients who are willing to follow strict sun protection instructions.

Dermoscopy helps in detecting the distribution of the pigment component of melasma; as well as observation of its vascular component [16]. In this study, baseline evaluation showed mainly granular pigmentation combined with pseudo-network pattern; less evident was the arcuate or annular pigmentation. Half of our patients showed background erythema, while telangiectasia was observed in one-quarter of them. Likewise, results were observed in a study on 100 melasma cases, where the reticuloglobular pattern was demonstrated in 35% of patients, an exaggerated pseudo-network with granular pigmentation in 18% of patient, archiform structures in 21% of patients, and telangiectasia in 35% of patients [17]. It has been recently demonstrated that melasma exhibited reticuloglobular pattern, which is mainly found in epidermal melasma; arcuate, honey-

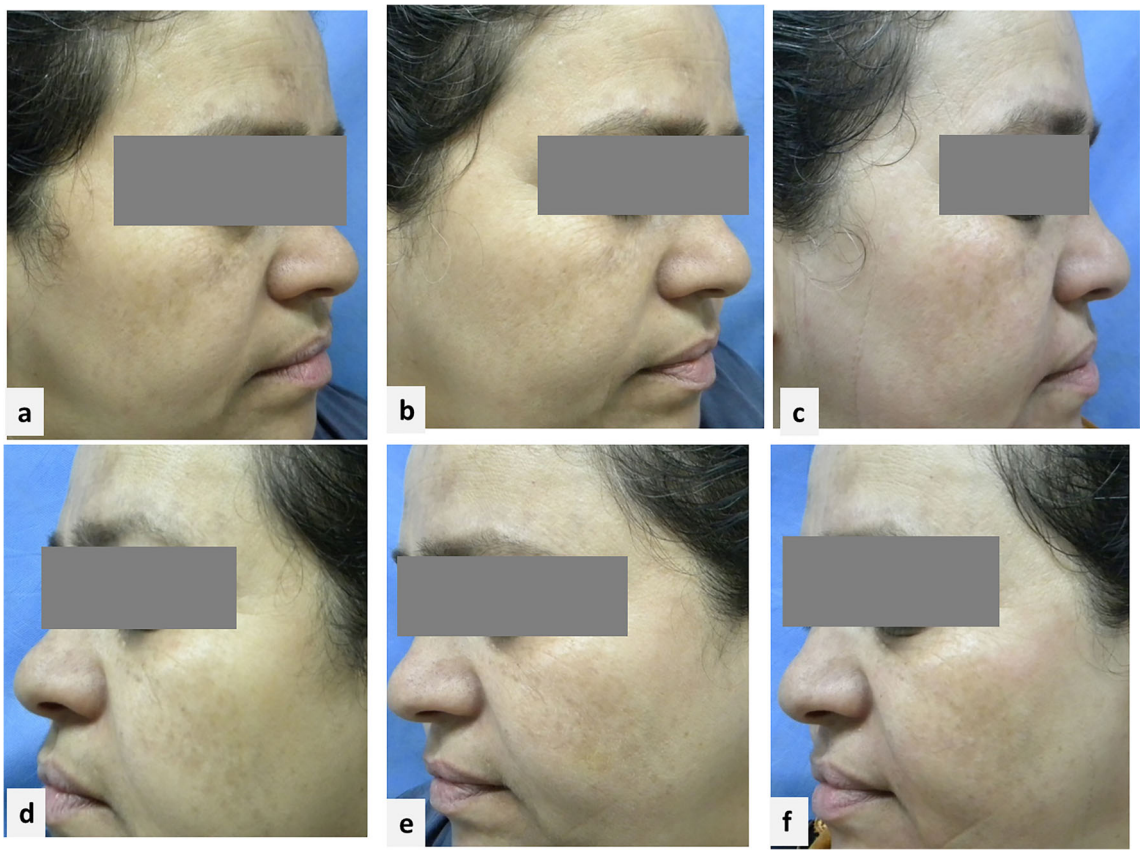

Fig. 2 Clinical images of Patient No: 18. Right side (side A 3 J/cm2, 2 passes): (**a**) week 0; (**b**) week 10 shows clinical improvement of pigmentation; (**c**) week 14 shows slight recurrence of pigmentation and presence of mild erythema. Left side (side B 1.5/cm2, 4 passes): (**d**) week 0; (**e**) week 10 shows mild improvement of the melasma; (**f**) week 14 shows same appearance of pigmentation as week 10

comb pattern, or dotted pattern mainly in dermal melasma; and structureless hyperpigmentation in mixed or dermal melasma [18]. Pseudoreticular network and reticuloglobular pattern are considered to represent an increased basal layer melanin pigment with or without flattening of rete ridges, respectively [13].

Following laser toning sessions, the granular pigmentation and pseudoreticular network became less, whereas arcuate and annular pigmented lines around the follicular openings became more obvious. The reduction of superficial pigmentation has unmasked the underlying deeper brown arcuate perifollicular pigmentation. Although Qs Nd:YAG laser beam can penetrate deeply through the epidermis into the dermis, it showed higher efficacy in reducing the superficial epidermal melanin pigment, whereas it was less capable of affecting the deeper annular periappendageal melanin pigment.

In this study, a higher percentage of our patients displayed telangiectatic blood vessels after treatment on both sides, although not statistically significant. The superficial brown

Table 1 Melanin index (MI) and erythema index (EI) at weeks 0, 10, and 14 in side A (3 J/cm^2, 2 passes) and side B (1.5 J/cm^2, 4 passes)

Time	Melanin index (MI)					Erythema index (EI)				
	Side A		Side B		*P* value between side A and side B	Side A		Side B		*P* value between side A and side B
	Mean ± SD	*P* value	Mean ± SD	*P* value		Mean ± SD	*P* value	Mean ± SD	*P* value	
W 0	642 ± 39	0.001	636 ± 43	0.001	0.634	452 ± 25	0.001	452 ± 16	0.001	0.475
W10	601 ± 52		601 ± 40		0.635	435 ± 10		440 ± 13		0.091
W14	620 ± 56		614 ± 40		0.769	442 ± 11		444 ± 11		0.438

W week; *SD* standard deviation; $P \leq 0.001$, highly significant; $P > 0.05$, insignificant

($n = 34$)

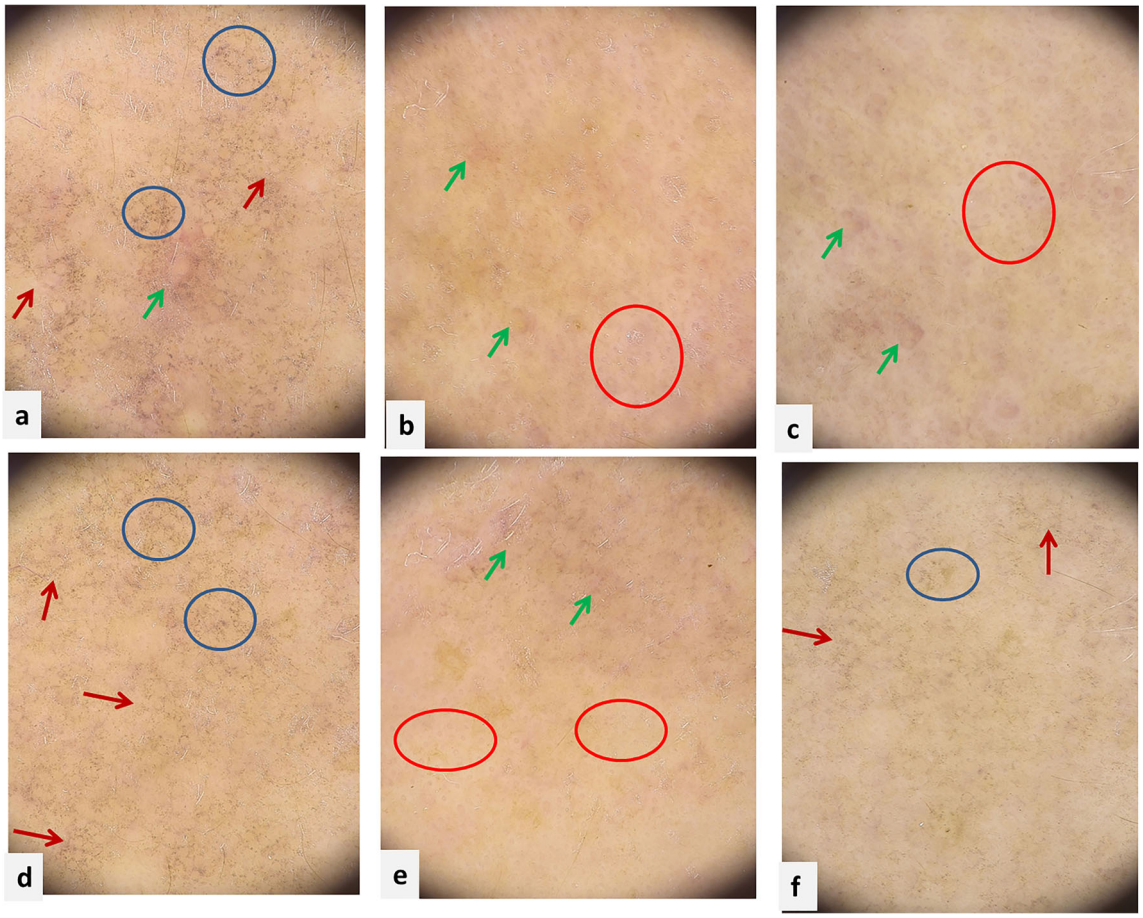

Fig. 3 Dermoscopic images of patient No 18: Right side (side A 3/cm2, 2 passes) that shows (**a**) week 0 shows reticular network (red arrows) with background erythema (green arrows) and dots of granular pigmentation (blue circles); (**b**) at week 10, background erythema is evident with faint perifollicular annular pigmentation (red circles). Reticular network and granular pigmentation became sparse; (**c**) week 14 shows background erythema is evident with faint perifollicular annular pigmentation. Left side (side B 1.5 J/cm2, 4 passes) which shows (**d**) week 0 reticular network (red arrows) and dots of granular pigmentation (blue circles); (**e**) week 10 shows background erythema (green arrows) and faint perifollicular annular pigmentation (red circles); (**f**) week 14 shows mild recurrence of reticular network and brown globular pigmentation (blue circle)

homogenous pigmentation became less in response to laser toning sessions, making the dermal vessels more evident on dermoscopy. Moreover, this confirms that Qs Nd:YAG laser toning does not affect the vascular component of melasma.

Conclusion

Both 3 J/cm^2 in 2 passes and 1.5 J/cm^2 in 4 passes parameters can be used biweekly effectively in treatment of melasma. However, the 1.5 J/cm^2 for 2 passes is preferred due to less associated pain and erythema. MSI and MI and EI are consistent methods for quantitative assessment of treatment response in cases of melasma, whereas dermoscopy is a reliable qualitative method for evaluating changes occurring in pigment and vascular patterns in response to therapy.

Limitation of the study is the relatively short follow-up period.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval The study was approved by the Dermatology Research Ethical Committee (Derma REC) at Faculty of Medicine, Cairo University; and standards of research ethics according to the Declaration of Helsinki were adopted.

Informed consent From all persons involved in this research, a written, informed consent to participate in the study and to be photographed was obtained.

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