A Randomized, Split-Face Clinical Trial of Low-Fluence Q-Switched Neodymium-Doped Yttrium Aluminum Garnet (1,064 nm) Laser Versus Low-Fluence Q-Switched Alexandrite Laser (755 nm) for the Treatment of Facial Melasma

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Background: Melasma is distressing for patients and challenging for physicians to treat. Clinical data from controlled comparative studies is lacking to support the efficacy, longevity, and safety of laser treatments for melasma.

Objective: Compare the efficacy and safety of low fluence Q-switched neodymium-doped yttrium aluminum garnet (1,064 nm) laser (Nd:YAG) versus low-fluence Q-switched alexandrite laser (755 nm) (QSAL) for the treatment of facial melasma.

Methods: Twenty male and female subjects with moderate to severe mixed-type melasma on both sides of the face were randomized to six, weekly treatments with the low-fluence Q-switched Nd:YAG laser on one side and the low-fluence QSAL to the other side. Two independent investigators conducted Modified Melasma Area and Severity Index (MMASI) evaluations and subjects completed self-assessment questionnaires at baseline, after three treatments and each follow-up visit 2, 12, and 24 weeks after the last treatment. Standardized digital photographs were taken at baseline and at each subsequent follow-up visit.

Results: One male and fifteen females, mean age of 43.4 (range 32–64) years, completed the 29-week study. Both laser treated sides showed a significant improvement in MMASI evaluations after two treatments (22% improvement on the QS-Nd:YAG, 17% QSAL) and each follow-up visit 2 (36% QS-Nd:YAG; 44% QSAL), 12 (27% QS-Nd:YAG; and 24% QSAL), and 24 weeks (27% QS-Nd:YAG; and 19% QSAL) after the last treatment, but no significant difference was seen between study groups at any visit. There was also no significant difference in subject evaluation of improvement between both treatment sides at any visit. There was also no significant difference in subject evaluation of improvement between both treatment sides at any visit. Both laser treated sides were tolerated well, and no serious adverse events were noted. Only one subject was taken out of the study due to development of post-inflammatory hyperpigmentation bilaterally.

Conclusion: Both low-fluence Q-switched Nd:YAG and low-fluence QSAL were equally effective at improving moderate to severe mixed-type facial melasma.

Limitations: This was a single-center trial and patients were not able to use complimentary lightening agents during the study. Lasers Surg. Med. 46:531–537, 2014. © 2014 Wiley Periodicals, Inc.

Key words: melasma; Q-switched Nd:YAG; Q-switched alexandrite laser; low fluence

INTRODUCTION

Melasma is an acquired, usually symmetric, facial hypermelanosis appearing as irregular light-brown to dark-brown macules and patches on the face, predominantly on the forehead, malar areas, and chin. It is particularly observed in women with Fitzpatrick skin types III to V [1], especially Asian and Hispanic women, although all skin types can be affected. Genetic factors, sun exposure, oral contraceptives, pregnancy and phototoxic or photoallergic drugs or cosmetics may play a role in the pathogenesis of this condition [2]; however, the etiology and pathogenesis are not yet fully understood.

Treatment modalities used for this condition include broad-spectrum (ultraviolet A + ultraviolet B) sunscreens, and a wide variety of topical agents including, but not limited to hydroquinone, retinoids, corticosteroids, azelaic acid, and kojic acid used alone or more commonly in combination. The need for long-term application and slow or limited treatment responses are major disadvantages of topical therapies [3]. Moreover, while topical agents may be effective for epidermal melasma, dermal, and mixed-
type melasma have pigment localized as deep as the mid-
dermis and are often refractory to topical monotherapy. Lasers and intense pulsed light sources in the treatment of melasma have been proposed as alternatives to help manage cases of recalcitrant melasma, yet they may be associated with post-inflammatory hyperpigmentation (PIH) and sometimes varying degrees of success [4,5].

Q-switched lasers have demonstrated efficacy in treating a variety of pigmented conditions such as ephelides, nevus of Ota, lentigines, and tattoos [6,7]. Recently, a new technique of repetitive low-fluence treatments over multiple sessions with a 1,064 nm Q-switched Nd:YAG laser has been reported to be effective for refractory melasma [6,8]. The 755 nm Q-switched Alexandrite laser (QSAL) has also been used for cutaneous pigmented lesions; however, its use for the management of melasma has been controversial. Although some studies have argued that QSAL is not effective against melasma and may induce side effects such as PIH, they used high fluences (5–7 J/cm²) and few treatment sessions [9]. In 2009, a Chinese group treated 32 patients with combination low-fluence 755 nm QSAL and QS 1,064 nm Nd:YAG lasers, showing marked to complete improvement of dermal or mixed-type melasma after multiple treatment sessions [10].

This study was conducted to evaluate and compare the efficacy of sequential low-fluence QS 1,064-nm Nd:YAG laser versus low-fluence 755-nm QSAL in the management of refractory, moderate to severe mixed-type melasma.

MATERIALS AND METHODS

The criteria for study participation included adult subjects aged 18–74 years of age with Fitzpatrick skin types I–IV having moderate to severe melasma on both sides of the face. Willingness to not use any topical products (skin lightening, retinoids, alpha/beta hydroxyl acids, salicylic acid, vitamins C and E, or antibiotics) on the facial area, or have chemical peels, laser or light treatments was mandatory throughout the duration of the study. Use of a mineral-based SPF 30 sunscreen (MD Solar Science, Norwalk, CT) provided for the study and avoidance of extended periods of sun exposure or the use of tanning beds were also required during the study.

IRB approval was obtained for this double-blinded, randomized, split-face, single-center, comparison study. The study was conducted according to ethical and regulatory principles from the International Conference of Harmonization. Prior to treatment, the subjects provided informed consent. The study was conducted in San Diego, CA from May 2012 to April 2013.

Treatment

The study was conducted over a 29-week period. In accordance with a pre-determined randomization schedule, subjects were randomized at baseline to either the low-fluence Q-switched Nd:YAG on one side of the face and the low-fluence QSAL on the other side. There were nine study visits: Baseline, Week 1, Week 2, Week 3, Week 4, Week 5, Week 7, Week 17, and Week 29. Six treatment sessions were performed at 1-week intervals, with follow-up at 2 weeks, 12 weeks, and lastly at 24 weeks after the last treatment session.

One side of the face was treated with the QS 1,064 nm Nd:YAG laser (Spectra, Lutronic Corporation, South Korea) using an 8 mm spot size, 1–2 J/cm² fluence (depending on tissue response), 5 Hz frequency and 1–8 passes until mild erythema developed. The other side of the face was then treated with the 755 nm QSAL (Accolade, Cynosure, Inc., Westford, MA) via a defocused 6 mm spot size in order to achieve an 8 mm spot size by adding 30 mm to the distance finger. The fluence distribution at 30 mm past the distance finger can be calculated based on the handpiece optical design. Figure 1 shows the calculated fluence distribution when the laser is set to 2.0 J/cm², with an effective fluence of 1.2 J/cm² near the spot center. The QSAL fluence was set at 1.8 J/cm², thereby treating with an effective fluence of 1.1 J/cm². One to two passes were performed at a 5 Hz frequency until mild erythema developed. After each treatment a SPF 30+ sunscreen was applied and strict sun protection was advised.

Clinical Efficacy

Two blinded investigators independently evaluated right and left sides of subjects’ faces using a Modified Melasma Area and Severity Index (MMASI) score (MASI score for each half of the face) at 1 week after the third treatment (Week 3) and 2 (Week 7), 12 (Week 17), and 24 (Week 29) weeks after the last treatment visit. Table 1 shows the MMASI used to score subjects melasma based percentage of the total area (A), darkness (D), and homogeneity (H) of melasma involving the forehead, cheek, and chin on each side of the face. To calculate the MMASI score, the sum of the severity grade for darkness (D) and homogeneity (H) was multiplied by the area (A) involved and by the percentages of the four facial areas (10–30%) using the following calculation for each side of

![Figure 1. The fluence distribution at 30 mm past the distance finger on a 6 mm handpiece when the QSAL laser is set to 2.0 J/cm².](image-url)
Subject evaluation of improvement was performed at 2 (Week 7), 12 (Week 17), and 24 (Week 29) weeks after the last treatment visit. Subjects, who were blind to the treatment received on each side of their face, evaluated the degree of improvement to the treatment areas using the following scores for each side of the face:

- \( C0 = \) worse,
- \( 0 = \) no change, \( 1 = \) poor (1–24% improvement in melasma), \( 2 = \) good (25–49% improvement in melasma), \( 3 = \) marked improvement (50–74% improvement in melasma), \( 4 = \) excellent improvement (75–100% improvement in melasma). This evaluation was made with subjects comparing their appearance with baseline photos.

**Safety Analyses**

The type (erythema, crusting, hypo- or hyperpigmentation), severity, duration, and frequency of each adverse event were tabulated for each treatment group.

**Clinical Photography**

Subjects were photographed at baseline and each follow-up visit using a digital camera (8.2 megapixels, Canon EOS 20 D, Tokyo, Japan), under the same lighting conditions. Digital photography with the Canfield VISIA system (Canfield VISIA) was taken at baseline and 2 (Week 7), 12 (Week 17), and 24 (Week 29) weeks after the last treatment visit, using the highest resolution in a consistent position.

**Statistical Analysis**

Statistical analysis was conducted on an intent-to-treat basis (all randomized subjects with at least one follow-up visit were included). All statistical tests were two-sided and interpreted at a 5% significance level. The primary analyses of efficacy were based on MMASI. A comparison between treatments was performed using two-sample \( t \) tests assuming equal variance and among groups using single factor ANOVA.

**RESULTS**

Nineteen females and one male subjects with a mean age 43.4 (range 33–64) years who met the inclusion/exclusion criteria were enrolled in the study, of which 2 were Fitzpatrick skin type II, 7 were skin type III and 11 were skin type IV. Fifteen females and one male subject completed the 29-week study. One subject dropped out to pursue treatment for her acne, and one subject was pulled from the study secondary to PIH that developed on both treated sides 1 week after her third treatment (Fig. 2). The remaining two subjects were lost to follow-up for the last two visits. The two treatment arms had similar baseline MMASI scores. The mean fluence used in the QS-Nd:YAG treated side was 1.4 J/cm² (range 1–1.9 J/cm²) and the effective fluence used on QSAL treated side was always 1.1 J/cm². The average number of passes used on the QS-Nd:YAG and QSAL-treated side until mild erythema developed was 5.02 and 1.72, respectively.

**Physician’s Assessment of Efficacy and Safety**

No significant change in grand mean MMASI scores between study arms was seen at any visit. One week after 2 weekly treatments (Week 3), the QS-Nd:YAG laser treated side showed a 22% improvement in MMASI score and the QSAL treated side showed a 17% improvement in MMASI score, which was not a statistically significant change from baseline (Fig. 3; \( P = 0.10 \) and \( P = 0.16 \), respectively). At
2 weeks after the sixth weekly treatment session (Week 7), the QS-Nd:YAG laser treated side showed a 36% improvement in MMASI score and the QSAL treated side showed a 44% improvement in MMASI score from baseline (Fig. 3; \( P = 0.007 \) and \( P < 0.001 \), respectively). By 12 weeks (Week 17) from the last treatment session, patients had some recurrence of their melasma, but the QS-Nd:YAG laser treated side still demonstrated a 27% improvement in MMASI score and the QSAL treated side still showed a 24% improvement in MMASI score (Fig. 3; \( P = 0.008 \) and \( P < 0.022 \), respectively). Significant results were maintained at 24 weeks from the last treatment session (Week 29) (Figs. 4 and 5).

When the data were further stratified to assess improvement in MMASI score based on Fitzpatrick skin Type, no significant changes were noted over time within the QS-Nd:YAG group for any skin type and no significant difference was noted between groups at any point. A significantly lower Modified MASI Score was noted from baseline over time in subjects with type III skin (\( P = 0.049 \)) on the QSAL side, otherwise, no other significant differences were noted within group and no significant difference between groups was seen at any point based on Fitzpatrick skin type.

**Subjects Assessment of Efficacy and Safety**

There were no significant differences in subject-reported efficacy between the two study arms at any visit (Table 2). Likewise, when data were stratified to assess subject-evaluated improvement based on Fitzpatrick skin type, subjects with type II skin reported greater improvement than those of type III skin at Weeks 3 and 4 (\( P = 0.005 \) and \( P = 0.002 \), respectively) and type IV skin at Week 29 (\( P = 0.028 \)) on the Nd:YAG treated side. On the QSAL treated side, subjects with type IV skin reported significantly greater improvement than those with type III (\( P = 0.047 \)) at Week 3. At Week 7, subjects with type II skin reported greater improvement than those with type III (\( P = 0.031 \)). At Week 17, subjects with type II and III skin reported significantly greater improvement than those with type IV skin (\( P < 0.001 \) and \( P = 0.022 \), respectively). At Week 29, subjects with type II skin reported significantly greater improvement than those with type 4 (\( P = 0.004 \)). No other significant differences were observed.

**Adverse Events**

Investigator assessments for tolerability showed clinically mild erythema, which was the end point of treatment, which typically lasted less than 24 hours. Otherwise there was no significant difference in the number or severity of adverse events between treatment arms.
DISCUSSION

Melasma is very difficult to treat and often refractory to treatment. Although the laser treatment of melasma has been relatively contraindicated, given the risk of photothermal stimulation of melanocytes and cutaneous inflammatory cascades, the use of QS-Nd:YAG laser with low energies and multiple sessions—often referred to as “laser toning”—has recently been demonstrated to be safe and effective in the management of the appearance of melasma [4,5,9]. This technique produces subcellular selective photothermolysis, leading to stage IV melanosome reduction with melanocyte sparing [11]. Decrease melanocyte function due to the downregulation of melanogenesis may also play a role [12]. Despite its safety, transient to long-term confetti-like hypopigmentation has been reported following multiple low-energy treatment sessions in Fitzpatrick skin types III–V [13–15]. Twenty subjects with epidermal or mixed-type melasma and Fitzpatrick skin types II–IV were treated with 8 weekly sessions using a QS-Nd:YAG laser in a study by Brown et al. [16]. Fluences of 2–4 J/cm² were delivered with 8–10 mm spot sizes. Mean MASI scores decreased progressively from baseline (4.43) to Week 8 (1.51) and were maintained at 1-month follow-up. Yet melasma flares were common by 3 months post-treatment.

The majority of study data regarding low-fluence Nd:YAG for dermal or mixed-type melasma, however, emanates from East Asian patients. Sim et al. [17] treated

Figure 4. Thirty-nine-year-old female (Fitzpatrick skin type II) treated with the QSAL laser on the right side (a) of her face and the Nd:YAG on the left side (b) of her face, at baseline (left), 2 weeks after six treatment sessions (middle), and 24 weeks after last treatment (right).

Figure 5. Fifty-two-year-old female (Fitzpatrick skin type IV) treated with the Nd:YAG laser on the right side (a) of her face and the QSAL on the left side (b) of her face at baseline (left), 2 weeks after six treatment sessions (middle), and 24 weeks after last treatment (right).
TABLE 2. No Significant Difference Between Study Arms Was Noted in Subject Evaluations of Improvement at Any Visit

<table>
<thead>
<tr>
<th>Nd:YAG laser</th>
<th>Week 3</th>
<th>Week 7</th>
<th>Week 17</th>
<th>Week 29</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worse (−1)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (6%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>No change (0)</td>
<td>9 (45%)</td>
<td>5 (26%)</td>
<td>7 (41%)</td>
<td>9 (56%)</td>
</tr>
<tr>
<td>Poor (1)</td>
<td>5 (25%)</td>
<td>7 (37%)</td>
<td>3 (18%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Good (2)</td>
<td>6 (30%)</td>
<td>3 (16%)</td>
<td>3 (18%)</td>
<td>3 (19%)</td>
</tr>
<tr>
<td>Marked (3)</td>
<td>0 (0%)</td>
<td>3 (16%)</td>
<td>2 (11%)</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Excellent (4)</td>
<td>5 (25%)</td>
<td>6 (30%)</td>
<td>4 (24%)</td>
<td>4 (25%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Q-switched alexandrite laser</th>
<th>Week 3</th>
<th>Week 7</th>
<th>Week 17</th>
<th>Week 29</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worse (−1)</td>
<td>2 (10%)</td>
<td>0 (0%)</td>
<td>1 (6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>No change (0)</td>
<td>8 (40%)</td>
<td>6 (32%)</td>
<td>8 (46%)</td>
<td>9 (56%)</td>
</tr>
<tr>
<td>Poor (1)</td>
<td>5 (25%)</td>
<td>3 (16%)</td>
<td>3 (18%)</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Good (2)</td>
<td>5 (25%)</td>
<td>6 (32%)</td>
<td>4 (24%)</td>
<td>4 (25%)</td>
</tr>
<tr>
<td>Marked (3)</td>
<td>0 (0%)</td>
<td>3 (16%)</td>
<td>1 (6%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Excellent (4)</td>
<td>1 (5%)</td>
<td>1 (5%)</td>
<td>0 (0%)</td>
<td>1 (5%)</td>
</tr>
</tbody>
</table>

-1 = worse, 0 = no change, 1 = poor (1–24% improvement in melasma), 2 = good (25–49% improvement in melasma).

50 subjects with 15 weekly sessions of QS-Nd:YAG using an 8 mm spot size and fluence of 2.8 J/cm² at 10 Hz. The endpoint of each treatment was mild erythema. Subjects and nonblinded investigator assessments demonstrated good to excellent improvement in the majority of subjects and digital measurements of pigmentation significantly improved during the study period. A combination of QSAL and QS-Nd:YAG was used by Wang and Liu [10] to treat melasma in 32 subjects. Twenty-one subjects had ≥90% improvement and 11 subjects had 68–89% improvement after a mean of 10.2 and 11.4 weekly sessions, respectively. However, neither study performed any significant amount of follow-up.

Wattanakrai et al. [15] randomized 22 Thai subjects with dermal and mixed-type melasma to 5 weekly sessions of QS-Nd:YAG (6 mm, 3.0–3.8 J/cm², 10 Hz) to one side of their face. Prior to starting laser treatment, subjects began applying 2% hydroquinone nightly to the full face. This and an SPF 60 sunscreen was continued throughout the study period to the full face. Sides treated with laser achieved a mean improvement of 92.5% in relative lightness index via colorimeter and 75.9% in mMASI score, compared with 19.7% and 24%, respectively, for the control side (P < 0.001). Subjects with Fitzpatrick skin type V were more likely to develop hypopigmented macules, and all subjects had melasma recurrence during the 12-week follow-up period. On the other hand, our prospective, randomized-controlled study demonstrated significant improvement in MMASI scores maintained up to 24 weeks following 6 weekly split-face, low-fluence treatments with Q-switched Nd:YAG and QSAL, with no significant difference between devices and no episodes of hypopigmentation.

A number of studies have evaluated the combination of low-fluence Q-switched lasers and topical agents. Jeong et al. [18] randomized 13 subjects to split-face treatment with QS-Nd:YAG and triple combination (TC) cream (4% hydroquinone, 0.05% tretinoin, 0.01% fluocinolone acetonide) for 8 weeks, at which point the treatments were reversed for another 8 weeks. TC cream was applied nightly. QS-Nd:YAG treatments were performed weekly with a 7 mm spot size, 1.6–2.0 J/cm² fluence, 5–7 nanosecond pulse duration, and 2 passes. MASI score reduction at 16 weeks was superior with TC cream followed by laser than with laser followed by TC cream (P < 0.05). Subject assessment of improvement was superior when laser treatments followed pretreatment with TC cream. A study by Bansal et al. [19] randomized 60 Indian subjects to 12 weeks of QS-Nd:YAG, 20% azelaic acid cream bid, or combination therapy. QS-Nd:YAG treatments were performed at weekly intervals with a 6–8 mm spot size, 0.5–1.0 J/cm² fluence, 10 Hz, and 10 passes. Combination therapy led to greater reductions in MASI scores than either treatment alone in epidermal (P < 0.05) and mixed-type melasma (P < 0.001); dermal melasma responded equally to QS-Nd:YAG with or without the addition of azelaic acid. The addition of 35–70% glycolic acid or Jessner’s peels, oral supplements like tranexamic acid, and procedures such as intense pulsed light and microdermabrasion to low-fluence Q-switched lasers may also enhance outcomes [20–24].

As seen in this study, laser only therapy for the management of melasma proved to be marginally satisfactory for patients with 40–48% having good or better perceived improvement at the end of treatment with the QS-Nd:YAG and QSAL, respectively; and about 35% noting to maintain this improvement in both treatment arms at 3 months and longer. To optimize results in the management of melasma, combination therapy with topical treatment may enhance and increase longevity of results, improving overall patient satisfaction. In addition, periodic laser and light therapy may be needed on an ongoing basis to manage melasma on a long-term basis.

In addition, while both the 1,064 and 755 nm wavelengths can be used in the management of melasma if fluence settings are properly chosen, caution should be exercised when using the 755 nm wavelength as it is absorbed more readily by melanin and traditionally has had higher risk of adversely effecting melanoma. In this study, although no increased adverse events were seen on the Q-switched lasers, only 1–2 passes were needed to achieve the endpoint of mild erythema, while up to 8 passes were sometimes needed to achieve the same endpoint with the QS-Nd:YAG. Attention to not overlap or accidentally pulse stack when using the QSAL is important, as it could mean a greater risk of overstimulating melanocytes, compared to the 1,064 nm QS-Nd:YAG.

CONCLUSIONS

This investigator and subject-blinded, randomized-controlled, split-face, comparative 28-week study of 2 Q-switched lasers demonstrated that QS-Nd:YAG and QSAL were equally safe and effective at improving moderate to
severe mixed-type facial melasma in Fitzpatrick skin types I–IV after multiple sessions with low fluences.

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