Prospective Studies of the Efficacy and Safety of the Picosecond 755, 1,064, and 532 nm Lasers for the Treatment of Infraorbital Dark Circles

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Background: Infraorbital dark circles result from a combination of factors. The fractionated picosecond 755 nm alexandrite laser and dual wavelength picosecond Nd:YAG laser have not been examined as a method of addressing infraorbital hyperpigmentation.
Objective: To determine the efficacy and safety of treatment of infraorbital dark circles using fractionated picosecond 755 nm and dual wavelength picosecond Nd:YAG laser.
Methods and Materials: These trials did not utilize a comparative design; rather, these were separate, prospective, open-label, evaluator-blinded trials utilizing two treatment regimens: (i) 19 adult subjects were treated in a single session with the dual wavelengths of 532 nm and 1,064 nm in consecutive passes using the fractionated lens; (ii) 10 adult subjects were treated using the picosecond 755 nm laser via the fractionated lens in three treatment sessions at 3 week intervals. Subjects in both studies were followed-up for blinded-investigator assessment of infraorbital hyperpigmentation, adverse events, and improvement compared to baseline.
Results: The dual wavelength picosecond Nd:YAG laser, blinded-investigator assessment did not demonstrate a significant improvement in infraorbital hyperpigmentation at day 60 ($P = 0.16$). The picosecond 755 nm alexandrite laser significantly improved infraorbital hyperpigmentation by day 42, with improvement maintained through day 132 ($P = 0.07$ and 0.00001, respectively). Adverse events were mild and temporary.
Conclusion: A single treatment with the fractionated picosecond 1,064/532 nm lasers did not produce a significant improvement in infraorbital hyperpigmentation. A series of three treatments with the fractionated picosecond 755 nm laser resulted in significant improvement in hyperpigmentation. Lasers Surg. Med. 50:45–50, 2018. © 2017 Wiley Periodicals, Inc.

Key words: aesthetics; lasers; picosecond; undereye circles

INTRODUCTION

Infraorbital dark circles result from a combination of factors including age-related skin laxity and volume loss, vascular prominence, fat pad herniation, medication use, and excessive pigmentation from both hemosiderin and melanocytic proliferation [1]. This multifactorial etiology often necessitates a multimodal therapeutic approach including volume restoration and laser stimulated increase in dermal collagen and epidermal thickness [2–6]. Hyperpigmentation of the delicate undereye skin can be especially problematic to treat due to the potential for mixed pigmentation presentation (hemosiderin vs. melanin) and the propensity toward post-inflammatory hyperpigmentation especially in darker skin types.

Picosecond laser has the potential to efficiently target excessive cutaneous pigmentation with shorter pulse durations, lower fluences, and reduced nonspecific photothermal damage as compared to previous pigment-specific quality-switched devices. The dual wavelength picosecond Nd:YAG laser emits both 532 and 1,064 nm wavelengths and thus has the potential to target both superficial and deep components of the infraorbital dark circle pathophysiology. In several published studies, the picosecond 755 nm alexandrite laser has demonstrated efficacy in photorejuvenation and treatment of benign pigmented lesions [7–12]. Both of these devices also offer a supplemental fractionated optic to safely deliver laser energy at higher focal fluences for improved clinical efficacy. The fractionated picosecond alexandrite laser has been previously reported to be effective in treating undereye pigmentation in a single case report [13]. However, there are no larger scale studies in the published

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literature examining the use of these lasers for treatment of infraorbital hyperpigmentation. In this article, we report the findings of two separate clinical trials analyzing the safety and efficacy of these two laser systems for treatment of infraorbital dark circles.

METHODS

Study Design

These were each prospective, open-label, evaluator-blinded clinical trials conducted separately at a single site. The studies were performed independently and were not designed to compare the devices or treatment regimens. Each study was approved by an independent Institutional Review Board.

Subjects

Nineteen healthy adult subjects were enrolled in the trial examining the dual wavelength picosecond Nd:YAG laser. Eleven healthy adult subjects were enrolled in the trial examining the picosecond 755 nm alexandrite laser. In each study, subjects were of Fitzpatrick skin types I through IV with at least a score of 3 on the Infraorbital Hyperpigmentation Severity Score (Table 1). Written informed consent and photographic release were obtained from each subject. All data were de-identified. Subjects were not compensated for their participation in this study.

Exclusion criteria for both studies included the presence of any pre-existing cutaneous or systemic illness; application of any energy device treatment to the infraorbital region within 3 months; application of any dermal filler to the infraorbital region within 6 months; facial resurfacing or deep chemical peels within 6 months; microdermabrasion (light or medium skin peel) treatment within 30 days; chemical peel, systemic steroids, non-ablative laser, light, or radiofrequency treatment within 3 months; use of topical lightening agents or retinoids within 14 days; the use of medications known to induce photosensitivity within 30 days. Subjects were instructed to refrain from any facial cosmetic procedures, including treatment for infraorbital dark circles, during the study period.

Female subjects were either of non-childbearing potential or were not pregnant at the time of enrollment and agreed to use a birth control method throughout the study duration.

Intervention

These were each prospective, open-label, evaluator-blinded clinical trials utilizing two distinct treatment regimens:

(1) Treatment with a single session using dual wavelength picosecond Nd:YAG laser (PicoWay, Syneron-Candela, Inc., Irvine, CA) in consecutive passes using the fractionated lens as follows: a single pass of 1,064 nm at 1.3 J/cm^2 and 5 Hz, immediately followed by a single pass of 532 nm at 0.16 J/cm^2 at 5 Hz for a total of 250 pulses between both eyes. Subjects followed up at 60 days post-treatment for blinded investigator assessment of infraorbital hyperpigmentation, adverse events and improvement compared to baseline.
(2) Treatment using the picosecond 755 nm alexandrite laser (PicoSure, Cynosure, Inc., Westford, MA) via a fractionated lens with a 6 mm spot size and 0.71 J/cm^2 fluence at 1–5 Hz in a single pass for a minimum of 50 pules per eye to no more than 150 pulses combined between both eyes. Subjects underwent three treatment sessions at 3 week intervals. Subjects were assessed at each treatment visit, day 72 (30 days post-final treatment), and day 172 (90 days post-final treatment) for blinded investigator grading of infraorbital hyperpigmentation, wrinkling, elastosis, adverse events and improvement compared to baseline.

Outcome and Statistical Analysis

Subjects who underwent treatment with the dual wavelength picosecond Nd:YAG laser were assessed at day 0 (when treatment was performed) and day 60. At each visit, photography was performed using both the Canfield Visia and the three-dimensional VECTRA system (Canfield Scientific Inc., Fairfield, NJ). A blinded investigator provided an Infraorbital Hyperpigmentation Severity score at days 0 and 60. Blinded investigators also assessed degree of improvement in infraorbital hyperpigmentation, while subjects completed a satisfaction questionnaire, on day 60. The presence and severity of treatment-related adverse events were recorded on a 5-point scale (none [0], trace [1], mild [2], moderate [3], and severe [4]).

Subjects who underwent treatment using the fractionated picosecond 755 nm alexandrite laser were assessed at

TABLE 1. Infraorbital Hyperpigmentation Severity Score

The homogeneity of the infraorbital hyperpigmentation rated on a scale of 0–4	0 = Normal skin color without evidence of hyperpigmentation 1 = Barely visible hyperpigmentation/specks of involvement 2 = Mild hyperpigmentation/small patchy areas of involvement $<$1.5 cm diameter 3 = Moderate hyperpigmentation/patches of involvement $>$2 cm diameter 4 = Severe hyperpigmentation/uniform skin involvement without any clear areas

day 0 (when the first treatment was performed), day 21 (second treatment), day 42 (third treatment), day 72, and day 132. At each visit, standardized photography was performed using a digital camera and the Visia system. A blinded investigator provided an Infraorbital Hyperpigmentation Severity score at each visit. A blinded investigator provided a Fitzpatrick–Goldman Wrinkling and Elastosis score at baseline, day 72 and day 132 (Table 2). Blinded investigators assessed degree of improvement in infraorbital hyperpigmentation (-1 = worse than baseline, 0 = no change from baseline, 1 = 0–24% improvement, 2 = 25–49% improvement, 3 = 50–75% improvement, 4 = 75–100% improvement) and subjects completed a satisfaction questionnaire on days 72 and 132. The presence and severity of treatment-related adverse events were recorded at each visit on the 5-point scale.

In both studies, statistical analyses were performed with Microsoft Excel 2013 and were conducted on an intent-to-treat basis. Continuous data were summarized with descriptive statistics such as percentages, means, ranges, and standard deviation, while frequencies were calculated for categorical variables. Statistical tests were performed using two-tailed Student's *t*-tests and interpreted at a 5% significance level.

RESULTS

Subjects

In the trial examining the dual wavelength picosecond Nd:YAG laser, 19 adult subjects who met inclusion criteria were enrolled. The mean age of enrolled subjects was 52.5 years (range, 33–81 years). Subjects were of a variety of Fitzpatrick skin types: 31.6% (6 of 19) subjects were skin type II, 42.1% (9 of 19) were skin type III, and 26.3% (5 of 19) were skin type IV. Mean hyperpigmentation severity at baseline was 3.1 ± 0.2. All subjects followed-up at day 60.

In the trial examining, the picosecond 755 nm alexandrite laser, 10 adult subjects were enrolled. The mean age of enrolled subjects was 43.6 years (range, 31–57 years). Of these subjects, 10% (1 of 10) were skin type II, 70% (7 of 10) were skin type III, and 20% (2 of 10) were skin type IV. Every subject had a baseline hyperpigmentation severity score of 3. In this study, one subject was lost to follow-up after the second treatment, another subject was lost to follow-up after day 72, and a subject withdrew prior to the third treatment when she became pregnant. Seven subjects returned for follow-up on days 72 and 132.

Efficacy of Fractionated Picosecond 1,064/532 nm

Blinded-investigator assessment of infraorbital hyperpigmentation did not demonstrate a significant improvement after treatment with the dual wavelength fractionated picosecond Nd:YAG laser (Fig. 1). At day 60, the mean Infraorbital Hyperpigmentation Severity Score was 2.74 ± 0.45, which was not significantly improved from the baseline score of 3.1 ± 0.23 ($P = 0.16$, Fig. 1).

Blinded-investigator assessment of improvement in hyperpigmentation at day 60 relative to baseline demonstrated that 10.5% (2 of 19) subjects achieved 25–49% improvement and 31.6% (6 of 19) showed 0–24% improvement (Table 3). However, investigators also determined that 31.6% (6 of 19) of subjects were unchanged compared to baseline, while 26.3% (5 of 16) of subjects were worse than baseline.

Efficacy of Fractionated Picosecond 755 nm

Blinded-investigator assessment of infraorbital hyperpigmentation demonstrated significant improvement in hyperpigmentation by day 42 (treatment 3). All subjects had an Infraorbital Hyperpigmentation Severity Score of 3 at baseline. At day 21, the mean score improved to 2.7 ± 0.48, but this change was not statistically significant. By day 42, the mean hyperpigmentation score decreased significantly to 2 ± 0.8 ($P = 0.0007$). This improvement was maintained at day 72 (2.42 ± 0.53, $P = 0.004$) and day 132 (2.17 ± 0.41, $P = 0.00001$, Fig. 2).

Blinded investigators also assessed improvement in hyperpigmentation relative to baseline at days 72 and 132. At day 30, 42.9% of subjects (3 of 7) demonstrated 0–24% improvement compared to baseline, while 14.3% (1 of 7) had 25–49% improvement, 14.3% (1 of 7) achieved 50–74% improvement, and 14.3% (1 of 7) reached 75–100% improvement. One subject demonstrated no change compared to baseline. At day 132, 85.7% of subjects (6 of 7) were graded as 0–24% improvement in hyperpigmentation compared to baseline (Table 3). The remaining subject demonstrated no change. The change in improvement from day 72–132 was not significant ($P = 0.14$).

Though blinded investigator-assessed wrinkling improved over the course of the study, the change was not statistically significant. The baseline mean wrinkling score was 2.1 ± 0.74. At day 72, the mean wrinkle score declined to 2.0 ± 0.82 ($P = 0.80$) and at day 132, the mean declined further to 1.86 ± 0.69 ($P = 0.50$).

TABLE 2. Fitzpatrick-Goldman Classification of Wrinkling and Elastosis

Class	Wrinkling	Score	Degree of Elastosis
I	Fine wrinkles	1–3	Mild (fine textural changes with subtly accentuated skin lines)
II	Fine to moderate-depth wrinkles, moderate number of lines	4–6	Moderate (distinct popular elastosis (individual papules with yellow translucency under direct lighting) and dyschromia)
III	Fine to deep wrinkles, numerous lines, with or without redundant skin folds	7–9	Severe (multipapular and confluent elastosis (thickened yellow and pallid) approaching or consistent with cutis rhomboidalis)

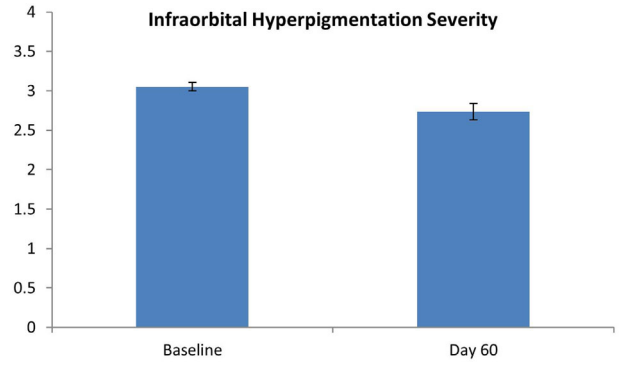

Fig. 1. Mean infraorbital hyperpigmentation severity scores for subjects treated with the dual wavelength picosecond Nd:YAG laser.

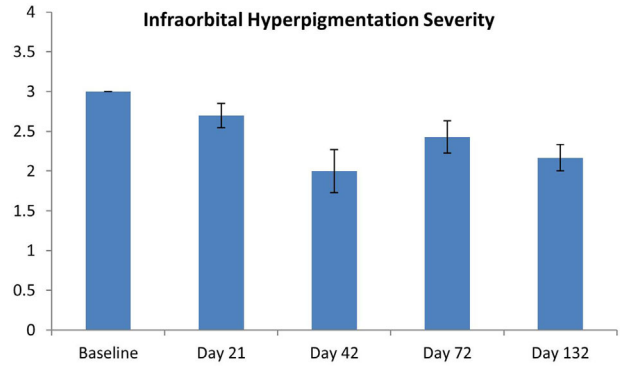

Fig. 2. Mean infraorbital hyperpigmentation severity scores for subjects treated with the picosecond 755 nm alexandrite laser.

Elastosis scores were unchanged throughout the study. The mean baseline elastosis score was 3.4 ± 1.26. At day 72, the mean score was 3.3 ± 1.6 ($P = 0.87$) and at day 132, the mean score was 3.6 ± 1.8 ($P = 0.82$).

Subject Satisfaction

Subjects treated with the fractionated picosecond 755 nm alexandrite laser evaluated their satisfaction at days 72 and 132. On day 72, 14.3% (1 of 7) of subjects were "satisfied," 42.9% (3 of 7) were "slightly satisfied," 28.5% (2 of 7) were "dissatisfied," and 14.3% (1 of 7) were "extremely dissatisfied." On day 132, 28.5% (2 of 7) were "satisfied" and 42.9% (3 of 7) were "slightly satisfied," while 28.5% (2 of 7) were "dissatisfied" with their clinical results (Table 4).

Subjects treated using the dual wavelength fractionated picosecond Nd:YAG laser provided a satisfaction score at day 60. At follow-up, 5.3% (1 of 19) of subjects were "extremely satisfied," 31.6% (6 of 19) were "satisfied," 31.6% (6 of 19) were "slightly satisfied," 10.4% (2 of 19) were "slightly dissatisfied," and 21.1% (4 of 19) were "dissatisfied."

Thus, at the final follow-up, 68.5% of subjects treated with the dual wavelength fractionated picosecond Nd:YAG and 71.4% of subjects treated using the fractionated picosecond 755 nm alexandrite laser were satisfied with their aesthetic outcome.

TABLE 3. Improvement in Infraorbital Hyperpigmentation Relative to Baseline

Improvement Relative to Baseline	Dual Wavelength Picosecond Nd:YAG (Day 60) (%)	Picosecond 755 nm Alexandrite (Day 132) (%)
Worse	26.3	0
Unchanged	31.6	14.3
0–24% Improvement	31.6	85.7
25–49% Improvement	10.5	0
50–74% Improvement	0	0
75–100% Improvement	0	0

Safety

Immediately following treatment with the dual wavelength regimen, the mean edema score was 1 ± 1.11, bruising was 1.42 ± 0.96 and pain/tenderness was 1.05 ± 0.97. All of these adverse events were resolved by day 60. Following treatment, investigators determined that 15.8% (3 of 19) subjects had trace and 15.8% (3 of 19) had mild hyperpigmentation distinct from their baseline infraorbital hyperpigmentation. On day 60, 21.1% (4 of 19) subjects had trace hyperpigmentation, 10.5% (2 of 19) subjects had mild hyperpigmentation, and 5.3% (1 of 19) subjects had moderate hyperpigmentation. Subjects in this study demonstrated no hypopigmentation, scarring, erosion/ulceration, or infection immediately post-treatment and on day 60.

At days 21, 42, 72, and 132, subjects treated with the picosecond 755 nm alexandrite laser demonstrated no pain/tenderness, infection, hyperpigmentation, hypopigmentation, scarring, erythema, edema, or bruising. Immediate post-treatment adverse events were not characterized.

DISCUSSION

Though infraorbital dark circles are a common complaint, there are currently no large scale studies in the literature examining the use of the dual wavelength fractionated picosecond Nd:YAG or fractionated picosecond 755 nm alexandrite lasers for treatment of infraorbital hyperpigmentation. These trials were not designed as a comparative study; rather, the two trials were conducted concurrently at a single institution with distinct treatment regimens based on the investigators' clinical experience and the characteristics of the devices.

TABLE 4. Subject Satisfaction at Final Follow-Up

Subject Satisfaction	Dual Wavelength Picosecond Nd:YAG (Day 60) (%)	Picosecond 755 nm Alexandrite (Day 132) (%)
Extremely dissatisfied	0	0
Dissatisfied	21.1	28.5
Slightly dissatisfied	10.4	0
Slightly satisfied	31.6	43.0
Satisfied	31.6	28.5
Extremely Satisfied	5.3	0

Subjects treated using the dual wavelength fractionated picosecond Nd:YAG regimen did not demonstrate significant improvement in hyperpigmentation by day 60. Further, 26.3% of these subjects were worse than baseline, likely due to the post-inflammatory hyperpigmentation evident in the adverse events data. Despite these blinded-investigator assessments, 68.5% of subjects were satisfied with their aesthetic outcome on day 60 (Fig. 3).

The fractionated picosecond 755 nm alexandrite regimen produced significant improvement in infraorbital hyperpigmentation by the third treatment on day 42, with results sustained through the end of the study at day 132. However, the improvement in hyperpigmentation from baseline, as assessed by blinded investigators, was mild, with 85.7% of subjects ultimately achieving 0–24% improvement (Fig. 4). The remaining subject was unchanged and no subjects were worse than baseline. These findings, in conjunction with the unremarkable adverse events assessments, suggest that post-inflammatory hyperpigmentation was not a significant issue in this treatment regimen. In contrast to the improvements observed in infraorbital hyperpigmentation, wrinkling, and elastosis were unchanged over the course of the study. Satisfaction at day 132 was high, with 71.4% of subjects stating they were satisfied with their results.

The overall lack of improvement in hyperpigmentation and the high rate of post-inflammatory hyperpigmentation in the dual wavelength fractionated picosecond Nd:YAG trial may be attributable to the settings used in only a single treatment session. Specifically, the use of 250 pulses delivered at 5 Hz may have resulted in a total energy density and velocity that triggered excessive risk of post-inflammatory hyperpigmentation. A larger trial utilizing a range of settings would better determine whether this device is efficacious for this indication, and may delineate the appropriate settings for such treatment. Optimization of settings using the fractionated picosecond Nd:YAG laser might include shortening the pulse duration from 750 to 500 ps, increasing fluence, and/or performing more treatments. Similarly, a larger trial of the fractionated picosecond 755 nm alexandrite

Fig. 3. A 62-year-old woman at baseline *(left)* and day 60 *(right)* after treatment with the dual wavelength fractionated picosecond Nd:YAG. The subject demonstrated 25–49% improvement in infraorbital hyperpigmentation and was "satisfied" with her results.

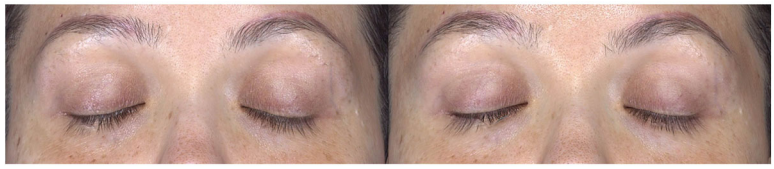

Fig. 4. A 40-year-old woman at baseline *(left)* and day 132 *(right)* after treatment with the fractionated picosecond 755 nm alexandrite. The subject demonstrated 0–24% improvement and was "slightly satisfied" with her results.

laser using a range of settings may also define a treatment regimen that achieves more significant improvement in infraorbital hyperpigmentation than that observed in this trial.

SUMMARY

In these investigator-blinded, prospective clinical trials, a single treatment with the fractionated picosecond 1,064/532 nm lasers did not produce a significant improvement in infraorbital hyperpigmentation and was found to induce a high rate of post-inflammatory hyperpigmentation. However, a series of three treatments with the fractionated picosecond 755 nm laser resulted in significant improvement in hyperpigmentation without post-inflammatory hyperpigmentation. Subject satisfaction in both trials was high.

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