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Effects of a fractional picosecond 1,064 nm laser for the treatment of dermal and mixed type melasma

Thep Chalermchai and Paisal Rummaneethorn

School of Antiaging and Regenerative Medicine, Mae Fah Luang University, Bangkok, Thailand

ABSTRACT
Background: Picosecond laser is a novel modality for pigmented skin disorders with extremely short pulse duration. Little is known about the effects of the picosecond laser in melasma. Objective: This study aimed to investigate the efficacy of fractional picosecond 1,064 nm laser in melasma treatment. Study design: A prospective, randomized, assessor-blinded, intra-individual split face comparative study. Methods: Female subjects with melasma were enrolled and received fractional picosecond 1,064 nm laser plus 4% hydroquinone cream on one randomly assigned side of the face; the results were compared to the use of hydroquinone cream only on the contralateral side. The modified melasma area severity index (mMASI) score, melanin index by Mexameter MX18®, participant satisfaction score by quartile rating scale, and the quality of life by the dermatology life quality index (DLQI) were evaluated over 12 weeks. Results: Thirty female subjects completed the protocol. The mean (± standard deviation, SD) mMASI score at the 12-week visit was significantly reduced in the picosecond laser-treated areas compared to controls (3.52 ± 1.4 and 4.18 ± 2.03 respectively; \( p = 0.035 \)). No differences were observed in the mean Mexameter melanin index, participant satisfaction score, and DLQI score. The observed adverse effects included transient mild erythema and mild skin desquamation. Conclusion: The addition of fractional picosecond 1,064 nm laser to 4% hydroquinone was effective and significantly better than 4% hydroquinone alone for the treatment of melasma.

Introduction

Melasma is an acquired skin melanosis that commonly affects facial areas including the forehead, cheeks, tip of the nose, and the chin area. Previous studies demonstrated a high prevalence rate of up to 35% in Latino population, predominantly affecting middle-age females (1,2). Management of facial melasma usually includes advice to avoid ultraviolet light and other aggravating factors such as specific photosensitizing medications and external hormonal replacement therapy (3). Topical anti-melanogenesis agents, such as hydroquinone, retinoic acid, alpha albutin, and glycolic acid (4) are the typical first-line treatments for melasma and work primarily by inhibition of the enzyme tyrosinase. However, the effects of topical treatments are often disappointing with minimal cosmetic improvement, unwanted side effects, and high rates of relapse (5,6). Cutaneous-pigmented laser has been proposed as an alternative and adjunctive treatment for certain skin hyperpigmentation conditions, including melasma (7,8). The main mechanism of the laser is to transmit high peak, photo-thermal energy into the skin, which specifically targets the melanin pigment resulting in so-called “selective photothermolysis” (9). The thermal effects of the laser break down melanin into tiny particles, which are then engulfed and removed by macrophages. Widely used pigmented laser technologies include Q-switch Ruby, Q-switch, Nd:YAG (Neodymium-doped yttrium aluminum garnet) and Q-switch alexandrite laser (7,9,10). In spite of some beneficial effects in melasma, the results are limited and unpredictable with adverse effects including pain, burning sensations and skin hypo- and hyper-pigmentation (10).

The picosecond laser system is a novel technology designed to minimize pain and post-laser skin discoloration caused by thermal effects (10,11). The picosecond laser is a laser system with multiple extremely short pulse durations of only 300–500 picoseconds (ps). Because of the short pulse duration, higher pulse energy can be delivered than with previous laser technologies, but with a lower associated thermal effect. At similar fluences, the photo-acoustic stress induced by picosecond lasers results in higher energies and greater fragmentation of melanin than that generated by the thermal stress of nanosecond lasers (12). Equally, treatment with shorter pulse durations allows satisfactory results to be achieved with lower fluences, so minimizing the risk of scarring and lessening damage to surrounding skin structures from thermal burn (13–16). Currently available wavelengths for picosecond laser are 532, 755, and 1064 nm (13,17,18).

The primary objective of this study was to compare the efficacy and safety of the fractional picosecond 1,064 nm laser in conjunction with a daily application of 4% hydroquinone
cream with 4% hydroquinone cream used alone for the treatment of deep or mixed type melasma. The secondary objectives were to evaluate changes in the melanin index by Mexameter MX18® measurement, patient treatment satisfaction score and reported quality of life by the Dermatology Life Quality Index (DLQI) questionnaire as well as to compare side effects between the two groups.

Materials and methods

This study is a prospective, randomized, assessor-blinded, intra-individual split face comparative study. Thirty Thai female subjects, aged between 18 and 65 years with Fitzpatrick’s skin type III or IV and a diagnosis of dermal or mixed type melasma were enrolled.

Inclusion criteria:

1. Female with bilateral melasma lesions
2. Aged between 18 and 65 years
3. Dermal or mixed type melasma, confirmed by Wood’s lamp test
4. Willing to participate in the study and to document their informed consent

Exclusion criteria:

1. Pregnancy or lactation
2. Outside work or other daily activities necessitating high exposure to UV light
3. Allergy to UV sunscreen or hydroquinone
4. Treatment with laser or chemical peeling within the preceding 3 months
5. Treatment with skin lighting medications or nutraceutical supplements within the preceding 4 weeks
6. Treatment with topical alpha arbutin, azelaic acid, kojic acid, ascorbic acid, topical retinoid, or hydroquinone within the preceding 4 weeks
7. Photosensitive conditions such as diabetes, thyroid disease, liver and kidney disease and photosensitive dermatosis
8. Active skin infection or acute dermatitis on skin sites used in the study
9. Inability to comply with the study protocol

Eligible subjects were assigned by blocked randomization with a block size of four to receive treatment with fractional picosecond 1,064 nm laser plus daily application of 4% hydroquinone cream on either the left or right side of their face. On the contralateral side, subjects applied 4% hydroquinone cream daily. This study was unable to blind either study investigators or subjects. However, expert assessors were blinded while determining study outcomes and blinding was maintained for personnel undertaking data analysis.

Study intervention and control:

- The study intervention refers to treatment with picosecond laser in addition to daily application of 4% hydroquinone cream.

Subjects underwent fractional picosecond 1,064 nm laser using the PicoWay® 1,064 nm laser at the prescription detailed below. After the laser treatment, the subjects were asked to apply 4% hydroquinone cream daily.

(1) The control intervention refers to treatment with once daily 4% hydroquinone cream application on the contralateral half of the face to the laser treatment site.

Subjects were evaluated at weeks 4, 8, and 12 after enrolment. At the enrolment visit, participants underwent a medical history, physical examination and targeted skin examination. The Mexameter® MX 18 was used to measure the melanin index three times at the same site and the mean score calculated. Photographic records were collected using three standard photo views, namely: one front view, and one view each from the left and right sides. Two independent, blinded dermatologist assessors determined modified melasma area severity index (mMASI) scores based on the photographs. Quality of life was assessed by asking subjects to complete the DLQI questionnaire.

The picosecond laser intervention was performed according to the following protocol: the skin on the side of the face randomized to receive the intervention was first numbed by applying EMLA® cream (lidocaine 2.5% and prilocaine 2.5%) covered by an occlusive dressing for 45 minutes before being washed off. The participants were then treated with a non-ablative fractional picosecond 1,064 nm laser (PicoWay®) at the following settings: 1,064 nm laser, resolve fractional mode, 100 dots per 6 × 6 mm diameter, fluence = 1.3–1.5 mJ per microbeam, pulse duration = 450 ps, 4% coverage per pass for 2–3 passes until mild erythema occurred as an endpoint with a total of 400–1000 shots, rate = 4 Hz. Following laser treatment, the investigators determined the incidence of any adverse effects such as redness and edema and also gave advice on how to perform skin self-care. A pain score was evaluated using a visual analog scale (VAS). Subjects were asked to apply 4% hydroquinone cream daily to the intervention side of their face.

For the control arm, on the side of the face contralateral to the laser intervention, subjects were asked to apply 4% hydroquinone cream daily. All subjects were also advised to apply UV sunscreen with a sun protection factor (SPF) of 60 daily to their whole face.

Week 4, 8, and 12 follow-up visits;

At the follow-up visits, the melanin index of both intervention and control sites was assessed using the Mexameter® MX 18; subjects were also asked to complete the DLQI questionnaire to determine quality of life and the participant treatment satisfaction score was recorded according to a quartile rating scale. Photographic records were also collected to evaluate the mMASI score.

Additional doses of fractional picosecond 1,064 nm laser (PicoWay®) were administered at the week 4 and 8 visits using the same parameters as at the enrolment visit. During the study period, all participants were advised to avoid any lightening creams, other laser procedures and any facial treatments or chemical peels.

Study Endpoints:

The primary endpoint of this study was to determine changes in the mMASI score at week 4, week 8, and week 12 compared to baseline and also to assess the difference in
proportions of individuals with at least 50% improvement between their baseline and week 12 visits (mMASI-50) between the two groups.

The secondary endpoints compared melanin index as determined using a Mexameter, global treatment satisfaction score using a quartile rating scale and subject quality of life using the DLQI, as well as adverse effects between the two groups at different time points.

Statistical analysis:
Comparisons of categorical data between combination treatment with fractional picosecond 1,064 nm lasers plus 4% hydroquinone cream and 4% hydroquinone cream alone were tested using the McNemar test. Paired student t-tests and repeated analysis of variance (ANOVA) were performed to compare continuous data including the mMASI score, Mexameter melanin index, DLQI score, and global satisfaction score between the two groups. A threshold for significance of 0.05 was used for all analyses. Statistical Package for the Social Sciences (SPSS) version 22.0 was used for data analysis. GraphPad Prism version 7.0 for Windows, GraphPad Software, La Jolla California USA was used for digital figure preparation.

This study was conducted according to the International Conference of Harmonization (ICH) Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki. The study protocol was submitted to the Mae Fah Luang University IRB for approval prior to participant enrolment.

Results
This study was approved by the independent Ethics Committee (IEC)/Institutional Review Board (IRB) of Mae Fah Luang University on 30 May 2016 and registered with ClinicalTrials.gov (identification number: NCT 3049059).

The study was conducted at Mae Fah Luang University Hospital, Bangkok, Thailand from 01 June to 31 December 2016. Thirty-three female subjects diagnosed with dermal or mixed type melasma were initially screened. Three subjects were excluded owing to mixed dermal melasma with Ota’s nevi (n = 1), unilateral facial melasmic lesions (n = 1) and clinical ochronosis from long standing use of topical bleaching agents (n = 1). Thirty subjects were enrolled and completed the protocol.

Demographic data
Thirty female subjects were enrolled. The mean age (SD) of the population was 47.5 (6.8) years (range: 33–62 years), with a mean (SD) time since diagnosis of clinical melasma of 6.3 (3.7) years.
Sixty percent (n = 18) of subjects were pre-menopausal; 40% (n = 12) were post-menopausal. 16.7% had Fitzpatrick’s skin type III; 83.3% had skin type IV. 36.7% of participants reported previous laser treatment (Table 1).

Primary outcomes
Modified melasma area severity index
At baseline, the mean (SD) mMASI score of the picosecond laser group was 9.46 (3.4), while that of the control group was 9.48 (3.4) (p = 0.975). Following the intervention, the mean mMASI score of both groups demonstrated a progressive and significant reduction from baseline (p < 0.001) over the 12 weeks of follow-up. On comparing the two groups at the endpoint visit (week 12), the picosecond laser group showed a significantly greater reduction in mean mMASI score than the control group of 3.52 (1.4) versus 4.18 (2.0) respectively (p = 0.035) (Figure 1).

Fifty percent improvement from the baseline of the modified melasma area severity index score (mMASI-50)
At 8 weeks after enrolment, a significantly greater proportion of the picosecond laser group (70%, n = 21) than the control group (43.3%, n = 13) (p = 0.04) showed a 50% or greater
improvement in mMASI from baseline. However, no significant difference was observed between the picosecond laser and control groups at end-point visit (week-12, $p=0.10$, Table 2).

### Secondary outcomes

#### Melanin index

There was no difference demonstrated in mean melanin index as assessed by Mexameter MX18® measurement at baseline and weeks 4, 8 and 12 as shown in Figure 2.

<table>
<thead>
<tr>
<th></th>
<th>Picosecond laser+4%HQ (n = 30)</th>
<th>4%HQ (n = 30)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>MASI-50 Week-4</td>
<td>10 (33.3)</td>
<td>8 (26.7)</td>
<td>0.57</td>
</tr>
<tr>
<td>MASI-50 Week-8</td>
<td>21 (70.0)</td>
<td>13 (43.3)</td>
<td>0.04</td>
</tr>
<tr>
<td>MASI-50 Week-12</td>
<td>23 (76.6)</td>
<td>17 (56.7)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

*Analyzed using the Chi-square test

At the week 4 visit, participant treatment satisfaction scores as assessed by a quartile rating scale were significantly better for the intervention than for the control group ($1.23 \pm 0.89$ vs. $0.70 \pm 0.65$ points respectively; $p = 0.011$) (Figure 3). However, the results at week 8 and week 12 did not demonstrate a significant difference between the two groups ($p = 0.28$ and $0.39$, respectively).

#### Participant quality of life

Both groups demonstrated improvements in their self-reported quality of life using the DLQI at week 4, week 8 and week 12 compared to baseline. However, no significant difference was apparent in self-reported quality of life between the two groups (Figure 4).

- **Adverse effects**

  The adverse effects of picosecond laser observed in this study included transient mild erythema ($n = 2$, 6.7%), mild skin desquamation ($n = 2$, 6.7%), and a mild burning sensation ($n = 1$, 3.3%). All adverse effects resolved without any treatment.

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**Table 2.** 50% improvement from the baseline of modified melasma area severity index score (MASI-50) at week 4, 8, and 12.

*Figure 2. *Analyzed using the analysis of variance (ANOVA) test with adjusted covariate data based on the baseline visit.

*Figure 3. *Independent student's t-test was used.
Discussion

Picosecond laser has been approved by the USFDA for use in tattoo removal (19,20). A systematic review by Reiter et al of the use of picosecond lasers in tattoo removal showed that 69–100% of tattoos demonstrated over 70% clearance of pigment after one to ten laser treatments (21). Side effects reported included immediate pain, skin hyperpigmentation, blister formation and transient skin redness. Picosecond lasers have also been employed with observed clinical benefit for the treatment of other skin pigmentation lesions, including in cutaneous argyria (22), minocycline-induced skin pigmentation (23) and nevus of Ota (24). A retrospective study by Chan JC et al investigated the treatment of cutaneous pigmented lesions using a picosecond 755-nm alexandrite laser in 13 Asian subjects over one to seven sessions of treatment (25). Pigmentary lesions treated in this study included Nevus of Ota, café-au-lait lesions and solar lentigine. The study reported that favorable outcomes could be seen in the Nevus of Ota and café-au-lait spots after 3–5 treatments. 4.8% of subjects in the study were observed to develop transient hypopigmentation following treatment. A previous study to determine the efficacy and safety of picosecond alexandrite laser with a specialized lens array for the treatment of photoaged décolletage found a significant improvement in dyspigmentation and skin texture at 1 and 3 months after initiation of treatment (26).

Little is known about the efficacy and safety of picosecond laser for the treatment of melasma especially in darker skin types, such as are found within Asian populations. A previous study looking at the effects of photo-thermolysis lasers in melasma demonstrated an improvement in mMASI score and patient satisfaction score in an Asian cohort after 3 sessions of treatment of melasma with low fluence Q-switched Nd: YAG 1064 nm laser and intense pulsed light; however, recurrence in the group was common and inevitable (27). Our study aimed to determine the efficacy and safety of picosecond alexandrite laser with a specialized lens array for the treatment of photoaged décolletage found a significant improvement in dyspigmentation and skin texture at 1 and 3 months after initiation of treatment (26).

week 4 than 4% hydroquinone cream alone, although this was not seen at the week 8 and 12 visits. Furthermore, treatment with picosecond laser also resulted in an improvement in quality of life at week 12 compared to baseline, but did not show a significant difference compared to treatment with 4% hydroquinone alone. This study is the first prospective clinical trial to demonstrate positive evidence for the use of picosecond laser in melasma. The study also describes improvements in quality of life following picosecond laser treatment and patient satisfaction with laser treatment. The safety profile of the intervention was impressive, with a median pain score of only 2.0 points (VAS; interquartile range: = 1–3 points) on a visual analog scale and limited adverse effects of only mild erythema, mild skin desquamation and a mild burning sensation. The major limitation of this study was the short follow up time, which prevented the investigators from fully determining the post-treatment recurrence of this disease.

CONCLUSION: The addition of fractional picosecond 1,064 nm laser to standard treatment with 4% hydroquinone is effective and significantly better than 4% hydroquinone alone for the treatment of mixed or dermal type melasma and demonstrates a good safety profile.

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Declaration of interest

The authors had no conflict of interest.

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