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Comparative Effectiveness of 20% Azelaic Acid with 1064-nm Nd:YAG Picosecond Laser vs Azelaic Acid Alone for Melasma Treatment in Thai Female Patients: A Split-Face Study

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Abstract

Melasma is one of the most concerning pigmented skin conditions usually found in females. Influenced by factors such as sunlight, occupation, gender, and drug use can aggravate the disease. This split-face clinical trial evaluates the effectiveness of picosecond laser in melasma treatment combined with topical azelaic acid compared to azelaic acid alone. The primary outcome of this study is the Hemi-MASI score, with secondary outcomes encompassing demographic data, physicians' global assessment, patient satisfaction score, and adverse events. Twenty Thai females, aged between 18 and 65, diagnosed with bilateral symmetrical malar-type melasma, were recruited for this study. The patients were administered with low fluence 1064-nm Nd:YAG picosecond laser three sessions every two weeks in combination with topical azelaic acid twice daily on the right side of the face while the left side received topical azelaic acid alone for 16 weeks. The mean decrease in Hemi-MASI score was 3.52%, 9.38%, and 19.94% on the combination side, while it was 1.93%, 7.89%, and 16.73% at the 8th, 12th, and 16th week respectively on the topical azelaic alone side. No severe side effects were reported with either picosecond laser or azelaic acid. The side effects were relieved without treatment. Consequently, the overall clinical outcome demonstrates improvement, as evidenced by satisfactory patient satisfaction scores. However, the mean Hemi-MASI score between the two sides was not statistically significantly different ($p>0.05$). In conclusion, combining the picosecond laser with azelaic acid alone in melasma treatment results in a better overall general outcome than the azelaic alone.

Keywords**:** *azelaic acid; melasma; 1064-nm Nd:YAG picosecond laser*

1. Introduction

Melasma is a chronic pigmented skin condition that is challenging to treat in the Thai population due to their darker skin type compared to the Western population. Typically, the lesion manifests as bilateral symmetrical hyperpigmented patches with irregular borders (Kang et al., 2019). Melasma has more prevalence in females, especially in the dark-skin type population (Ogbechie-Godec, & Elbuluk, 2017). Associated risk factors include ultraviolet radiation exposure, pregnancy (Qazi et al., 2017), oral contraceptive pill usage, and also from genetic predisposition (Lee, 2014; Wu et al., 2021).

Currently, the most successful modalities in treating melasma involve sun protection and applying topical medication such as hydroquinone to inhibit the Tyrosinase enzyme mechanism. However, one serious side effect of hydroquinone is ochronosis, clinically presented as hyperpigmented caviar-like macules and is rarely treatable

(Ogbechie-Godec, & Elbuluk, 2017), as well as leukoderma (Farshi, 2011).

Topical azelaic acid, a non-phenolic compound derived from Pityrosporum ovale, is one of the Tyrosinase inhibitors. Its mechanism of action involves DNA synthesis blockage and mitochondrial oxidoreduction in abnormal melanocytes without attacking the normal melanocytes (Küçük, 2018; Farshi, 2011). Applying topical azelaic acid is considered one of the safe options for treating melasma in pregnant women and rarely causes ochronosis.

The picosecond laser, a newer generation of laser with a short pulse duration, contributes to targeted pigment destruction. Its photoacoustic effect is more pronounced than its photothermal effect, resulting in less surrounding tissue injury and reduced post-inflammatory hyperpigmentation development compared to conventional Q-switched laser (Kamal et al., 2021; Wong, 2019). At present, the available wavelengths used for picosecond lasers are 532 nm, 755 nm, and 1064 nm (Trivedi et al, 2017). Nevertheless, the number of previous studies about picosecond lasers and melasma is quite small compared to other old-fashioned lasers (Trivedi et al, 2017).

A study assessing the effects of a fractional picosecond 1064 nm laser for the treatment of melasma in Thailand demonstrated that combining picosecond laser with 4% hydroquinone was more effective than 4% hydroquinone alone in melasma treatment. The outcomes were measured using the mMASI score, dermatology life quality index, and melanin index (Chalermchai, & Rummaneethorn, 2018). This suggests that adjunctive therapy of picosecond laser with topical melasma medication may enhance clinical outcomes.

Our research objective is to compare the effectiveness of 20% azelaic acid with low-fluence 1064 nm Nd: YAG picosecond laser versus 20% azelaic acid alone in treating melasma in Thai female patients as a split-face prospective study.

2. Objectives

To compare the effectiveness between 20% azelaic acid with low-fluence 1064 nm Nd: YAG picosecond laser and 20% azelaic acid alone in the treatment of melasma in Thai female patients as a split-face prospective study.

3. Materials and methods

3.1 Materials and Equipment

1) A low-fluence 1064-nm Nd:YAG pico-second laser (Picoway®, Candela)
2) Case record form
3) VISIA® skin analysis equipment
4) 20% azelaic acid cream
5) Skin Intelligence SPF 30 sunscreen

3.2 Procedural process

This prospective, non-randomized, controlled split-face trial was conducted at the Institute of Dermatology, Bangkok, Thailand, with approval from the ethics committee of the Institute of Dermatology. All subjects completed a written consent form before starting the project. The sample size was 20 subjects calculated from two dependent means formula with a 30% dropout rate, as determined by the n4Studies application (Ngamjarus, & Chongsuvivatwong, 2016).

Inclusion Criteria:

1) Thai female patients aged 18-65 years old.
2) Diagnosed with malar-type melasma on both sides of the face, symmetrically.
3) Ability to attend the research and willingness to participate as a subject, including providing consent.

Exclusion Criteria:

1) Use of oral contraceptive pills or hormone replacement therapy.
2) Pregnancy or lactation.
3) Underlying disease of autoimmune diseases.
4) Having thyroid diseases.
5) Allergy to preservatives in azelaic acid or topical melasma treatment.
6) Receiving laser treatment on the face within six months.
7) Applying topical melasma treatments, for example, kojic acid, hydroquinone, alpha arbutin, and whitening agents within four weeks.
8) Being treated by chemical peeling agents or using tranexamic acid or vitamin C within three months.
9) Taking or applying retinoids within twelve months.
10) Active asthma.
11) Use of antiepileptic drugs.
12) Presence of active skin inflammation/ infection or any other skin disease, for instance, allergic dermatitis, cellulitis, erysipelas, or herpes infection on the face.

In this split-face trial, all participants were requested to apply Skin Intelligence SPF 30 sunscreen

using a dosage of 2 fingertip units (FTU) to the entire face once a day for a week prior to the study and persisting throughout the 16-week study period.

On the right side of the face, the low fluence 1064-nm Nd:YAG picosecond laser (Picoway®, Candela) was done with the laser parameter as follows: pulse duration 450 ps, spot size 10 mm, fluence 0.4-0.8 J/cm^2, repetition rate 8 Hz every two weeks for three sessions. The endpoint of the laser is mild erythema. After the laser treatment, moisturizer was applied to the face with sunscreen. Concurrently, participants were instructed to self-application of 20% azelaic acid cream twice daily on the melasma non-laser-treatment day, not exceeding 0.5 FTU/side/times of the melasma throughout the research period. On the left side of the face, subjects applied 20% azelaic acid cream twice daily on the melasma non-laser-treatment day for 16 weeks.

3.3 Assessment method

Follow-up evaluation was assessed at 8th week, 12th week, and 16th, facilitating an evaluation through multiple outcomes:

1) Hemi-MASI score was calculated from the subjects' photographs taken using VISIA® skin analysis equipment. These scores were adjudicated independently by three dermatologists who were not associated with this study. Hemi-MASI was compared between two sides of the face using a multilevel model at each follow-up interval.

2) The physician's global assessment (PGA) was evaluated by the same three dermatologists who were not associated with this study, utilizing the Intraclass Correlation Coefficient (ICC) to determine the inter-rater reliability and the consistency of their evaluations.

3) Patient satisfaction scores were evaluated by patients rating their satisfaction on a 5-point Linkert scale (5=strongly improved, 4=moderate to strongly improved, 3=moderately improved, 2=slightly improved and 1=not improved) using the case record form.

4) The side effects were recorded after three laser treatment sessions.

Additionally, demographic data such as age, underlying disease, Fitzpatrick skin types, and side effects were declared as descriptive data reporting frequency, percentage, mean, and standard deviation. The statistical analysis of the collected data was conducted using SPSS and Stata program, with a p-value less than 0.05 was considered statistically significant.

4. Results

A total of 20 patients completed the study. The mean age of patients was 48, ranging from 31 to 60. The most common underlying diseases were allergic rhinitis and hypertension. In this study, the Fitzpatrick skin types were type III (45%) and IV (55%) as shown in Table 1.

Table 1 Demographic data including age, underlying disease, and Fitzpatrick skin type (n=20)

Demographic data	Results
Age, mean (standard deviation; SD), years	48 (8)
- range, years	31-60
Underlying disease	
- allergic rhinitis, n (%)	3 (15%)
- hypertension, n (%)	3 (15%)
- dyslipidemia, n (%)	1 (5%)
- gastritis, n (%)	1 (5%)
- thalassemia trait, n (%)	2 (10%)
- none, n (%)	13 (65%)
Fitzpatrick skin type	
- type III, n (%)	9 (45%)
- type IV, n (%)	11(55%)

Table 2 The mean hemi-MASI score

	Picosecond with azelaic side	Azelaic side	p value
Baseline	5.115 ±1.819	5.450±1.903	0.559
8th week	4.935±1.7	5.345±1.815	0.457
12th week	4.635±1.742	5.020±1.800	0.481
16th week	4.095±1.829	4.538±1.871	0.437

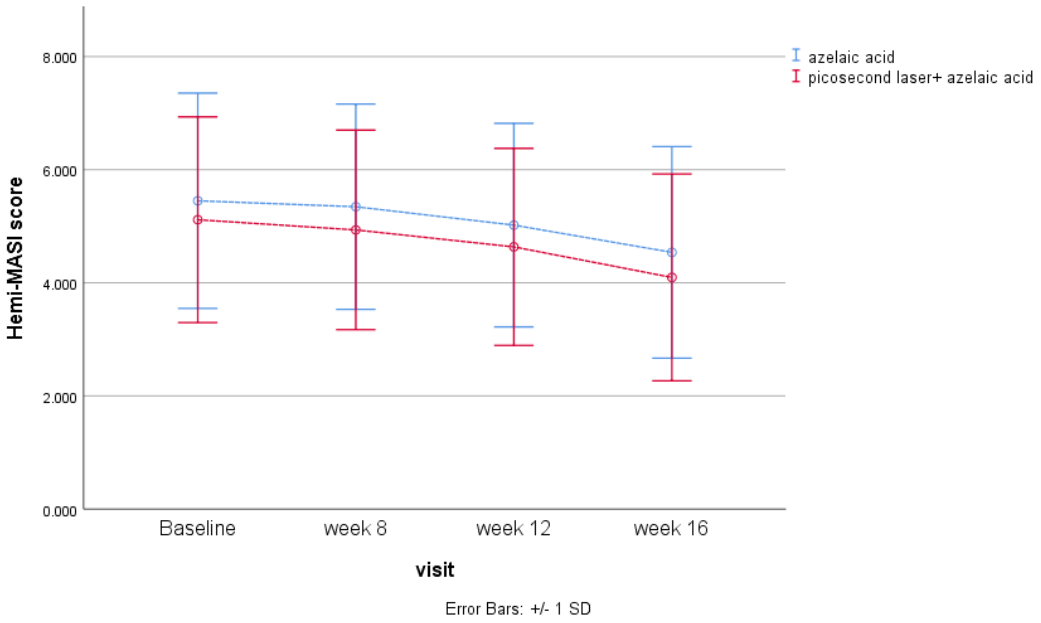

Figure 1 Mean Hemi-MASI score between two sides of the face at baseline, 8th week, 12th week, and 16th week

The mean hemi-MASI score was 5.115 ±1.819 on the right side, while it was 5.450±1.903 on the left side at the beginning of the study. The hemi-MASI on the right side was 4.095±1.829 and 4.538±1.871 at 16 weeks. The results showed that there was a lower number of Hemi-MASI scores for both combination-treated sides in the 16th week of the study, but it was not statistically significant ($p>0.05$), see Table 2 and Figure 1.

The mean physician's global assessment (mean PGA) from three dermatologists were 1.55±0.60, 1.85±0.67, and 2.25±0.72 out of 5 with ICC = 0.627 indicating moderate reliability (Koo, & Li, 2016) at the 8th week, 12th week, and 16th week, respectively on the picosecond laser and azelaic side while the mean PGA were 1.20±0.41, 1.65±0.59 and 2.15±0.75 at the 8th week, 12th week, and 16th week, respectively on azelaic side.

For the side treated with picosecond laser combined with azelaic acid, patient satisfaction scores were predominantly graded as 4 at each follow-up, as described in Table 3. For the side treated with azelaic acid alone, patient satisfaction scores were mostly graded as 3 at the first follow-up, whereas scores of 4 were recorded in the 12th and 16th weeks, as seen in Table 3. Clinical pictures of a patient are shown in Figure 2, demonstrating improvement in melasma in the right picture (at the end of the study) compared with the left picture (at baseline). At the 16-week follow-up, the melasma on the right side of the face (treated with laser combined with azelaic acid) was lighter than on the left side (treated with azelaic acid alone).

Table 4 shows that the overall mean patient satisfaction score was better on the picosecond laser with an azelaic side when compared with the azelaic side. The mean patient satisfaction score is 4±1, 4±1, and 4±1 at the 8th, 12th week, and 16th week, consecutively on the picosecond laser with azelaic side whereas on the azelaic side, there is 3±1, 4±1, and 3±1 at the 8th, 12th week, and 16th week which was better in the picosecond laser with azelaic acid side.

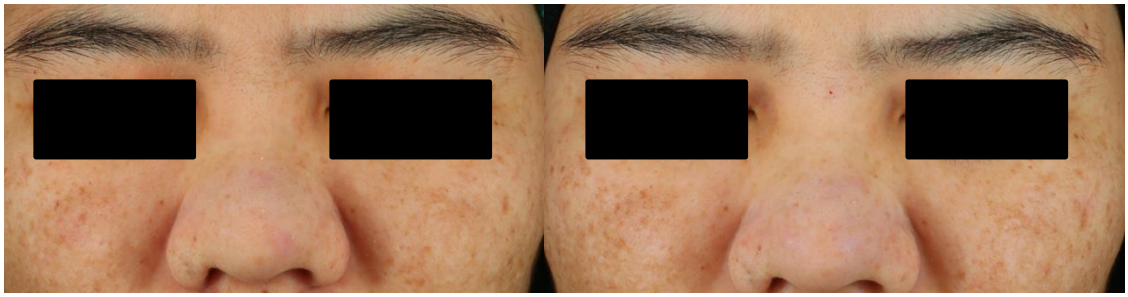

Figure 2 Clinical pictures of a patient at baseline (left) and after 16-week of follow-up (right)

Table 3 Patient satisfaction score at 8th week, 12th week and 16th week from baseline

Patient satisfaction score	Picosecond laser with azelaic acid			Azelaic acid alone		
	8th week	12th week	16th week	8th week	12th week	16th week
1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
2	0 (0%)	0 (0%)	0 (0%)	2 (5%)	2 (5%)	2 (5%)
3	6 (15%)	1 (2.5%)	1 (2.5%)	10 (25%)	8 (20%)	6 (15%)
4	12 (30%)	12 (30%)	14 (35%)	7 (17.5%)	8 (20%)	12 (30%)
5	2 (5%)	7 (17.5%)	5 (12.5%)	1 (2.5%)	2 (5%)	0 (0%)

Table 4 The mean patient satisfaction score at 8th week, 12th week, and 16th week

	Week	Mean ± SD
Picosecond laser with azelaic acid	8	4±1
	12	4±1
	16	4±1
Azelaic acid	8	3±1
	12	4±1
	16	3±1

The patients' side effects were burning and stinging sensations from azelaic acid for 5 patients (12.5%) at the 2nd week, 1 patient (2.5%) at the 4th week, 1 patient (2.5%) at the 8th week, and 1 patient (2.5%) at the 12th week. The symptoms are mild and resolved without any treatment.

Some patients developed the side effect of erythema on the laser-treated side. 4 patients (10.5%) at the 2nd week and 1 patient (2.5%) at the 4th week. The symptoms and erythema are relieved after cold compression. The erythema severity was also graded as mild erythema.

5. Discussion

The mean Hemi-MASI percentage reduction begin to be visible at the 8th week from the baseline on the combination side compared to the topical azelaic alone side. Still, it is not statistically significant on both sides. The mean patient satisfaction score is better on the combined side when compared with the azelaic acid alone. The mean physician's global assessment is superior on the combined side compared to the azelaic acid alone.

The safety profile of this study is satisfying for both low fluence 1064-nm Nd:YAG picosecond laser and azelaic acid since they are very mild and reversible. The serious adverse effects, such as dyspigmentation or hyperpigmentation, are not found in this study.

In a previous study, the effects of a fractional picosecond 1064-nm laser on the treatment of melasma were evaluated using the mMASI score, dermatology life quality index, and melanin index. The study showed that a picosecond laser combined with 4% hydroquinone was more effective than 4% hydroquinone alone (Chalermchai, & Rummaneethorn, 2018). Compared to previous studies, our study had a longer follow-up period, 16 weeks from the baseline. The mode of the laser is non-fractional

mode with fewer adverse events due to less epidermal injury. The overall clinical of melasma was improved, as indicated by the patient satisfaction score regardless non-significant results in hemi-MASI score.

At the future date, researchers can implement and amend the protocol by engaging more patient samples as to meet the proper accuracy. Moreover, various parameters in terms of the number of sessions, interval, fluence, spot size, and mode of the laser, which are non-fractional or fractional mode, can be adjusted to conduct the new protocol. They can also provide treatment protocols using a low-fluence picosecond laser with other topical melasma medications such as kojic acid, ascorbic acid, glycolic acid, etc. Additionally, the researcher can adapt the picosecond laser combined with topical medications to treat other pigmented diseases.

6. Conclusion

In conclusion, this study demonstrated the effectiveness of malar-type melasma treatment as a split-face, non-randomized clinical trial in Thai female patients aged 31 to 60 in the Institute of Dermatology, Bangkok, Thailand. Although the Hemi-MASI score between the two sides of the face is not statistically significantly different, the overall clinical of the patients is improved. The patient satisfaction score is higher on the side treated with the laser combined with the topical azelaic than for the side treated with the topical azelaic side only. The safety profile is also satisfying due to minimal side effects that can be alleviated without invasive procedures. This study is beneficial for melasma treatment, especially in darker skin type patients, which can be adapted by implementing the 1064-nm Nd:YAG picosecond laser with the approved topical melasma medication.

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