A comparison of Q-switched alexandrite laser and intense pulsed light for the treatment of freckles and lentigines in Asian persons: A randomized, physician-blinded, split-face comparative trial

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Background: Q-switched (QS) pigmented lasers and intense pulsed light (IPL) successfully treat pigment disorders.

Objective: We sought to compare efficacy and side effects of QS alexandrite laser (QSAL) and IPL for freckle and lentigo treatment in Asians.

Methods: In all, 15 patients with freckles and 17 patients with lentigines were treated randomly with one session QSAL in one cheek and two sessions IPL in the other cheek at 4-week intervals. Efficacy was determined using a new pigmentation area and severity index score.

Results: All patients experienced improvement ($P < .0001$). Postinflammatory hyperpigmentation developed in one patient with freckles and 8 patients with lentigines after QSAL. No postinflammatory hyperpigmentation occurred after IPL. Freckles achieved greater improvement after QSAL than IPL ($P = .04$). In lentigines, the results after IPL were better than QSAL among those with postinflammatory hyperpigmentation after QSAL.

Limitations: Limitations include a small case number and short follow-up period.

Conclusion: QSAL was superior to IPL for freckle treatment. IPL should be used for lentigines in Asian persons. (J Am Acad Dermatol 2006;54:804-10.)

Freckles and lentigines are common cutaneous pigmented lesions in Asians with similar clinical manifestations. Freckles occur in early adolescence, but lose their prevalence with age. Freckles become equally distributed, and are relatively uniform in size and color. Histopathology shows freckles as epidermal hypermelanosis.

Abbreviations used:

IPL:	intense pulsed light
Nd:YAG:	neodymium:yttrium-aluminum-garnet
PIH:	postinflammatory hyperpigmentation
PSI:	pigmentation area and severity index
QS:	Q-switched
QSRL:	Q-switched ruby laser
QSAL:	Q-switched alexandrite laser

Lentigines occur after adolescence, and increase in prevalence and number with age. In addition, lentigines become unevenly localized and vary in size and color. Histopathology reveals that lentigines are variable epidermal and melanocytic hyperplasia.[1,2] It is not difficult to distinguish between these two entities on thorough patient history and physical examination. Treatments are often requested for cosmetic purposes.

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Table I. Baseline characteristics of the patients

	Freckles (n = 15)			Lentigines (n = 17)		
Age, y	36.0 ± 8.6			45.9 ± 5.6		
Age onset, y	12.0 ± 3.2			31.9 ± 5.9		
Skin types, III/IV	7/8			4/13		
Treatment modalities	**QSAL**	**IPL**	***P* value***	**QSAL**	**IPL**	***P* value***
Baseline severity of pigmentation						
Area value, 0-6	2.6 ± 0.9	2.7 ± 0.8	.3	2.1 ± 0.8	2.1 ± 0.7	1.0
Darkness value, 0-4	2.6 ± 0.6	2.6 ± 0.6	1.0	2.4 ± 0.6	2.4 ± 0.6	1.0
Density value, 0-4	2.3 ± 0.6	2.4 ± 0.5	.3	1.9 ± 0.7	1.8 ± 0.6	.6
PSI score, 0-48	13.2 ± 7.0	13.9 ± 6.5	.1	9.8 ± 5.7	9.5 ± 5.3	.9

IPL, Intense pulsed light; *PSI*, pigmentation area and severity index; *QSAL*, Q-switched alexandrite laser.
*Difference between sides treated with QSAL and IPL.

Before the advent of lasers, treatment modalities of pigmented disorders included neglect, covering the skin with makeup, chemical bleaching, peeling, cryosurgery, dermabrasion, and electrodesiccation. In the past decade, several lasers with wavelengths strongly absorbed by melanin and nanosecond pulse durations have been shown to treat pigmented lesions effectively and quickly. These include the Q-switched (QS) neodymium:yttrium-aluminum-garnet (Nd:YAG) laser,[3,4] QS ruby laser (QSRL),[5] and QS alexandrite laser (QSAL).[6,7] However, certain side effects, especially postinflammatory hyperpigmentation (PIH), are common in Asian people after laser therapy.[8] Double-frequency QS Nd:YAG laser with a 532-nm wavelength is appropriate for destructing melanin-containing cells in the epidermis,[9] although its use is associated with higher risk of PIH compared with QSRL and QSAL.[6]

Intense pulsed light (IPL) is a noncoherent, broad-spectrum light that allows variations in pulse length, mode, delay between pulses, and fluence. It has been used to treat pigmented lesions with promising results in recent years.[10-13] Superficial pigmented lesions respond better than deeper lesions.[10] The lack of PIH is the overwhelming advantage of IPL; however, multiple treatment sessions are required to achieve excellent clearance.

QS pigmented lasers and IPL have been very popular worldwide, and have been the main treatment modalities for pigmented lesions in Taiwan during recent years. However, no randomized study comparing these treatments has been reported in the literature. Therefore, we designed the first randomized, physician-blinded, split-face comparative study of the efficacy and side effects of QSAL and IPL for the treatment of freckles and lentigines in Asian persons.

METHODS

Thirty-two Taiwanese women with freckles (n = 15) and lentigines (n = 17) were enrolled in the study. Freckles and lentigines were diagnosed clinically by 3 investigators based on a criteria reported by Bastiaens et al.[2] Lentigines intermingled with freckles and other pigmented disorders, such as melasma and nevus zygomaticus, are common in Asian women. These patients were excluded from the study. Patients who were pregnant or lactating, on birth control pills or hormone replacement therapy, and participated in major outdoor activities were excluded. Patients who used bleaching agents such as hydroquinone cream and those who received lasers or IPL treatment within 1 year of enrollment were also excluded. Patient history regarding age of onset of pigmented lesions and Fitzpatrick skin types were recorded. The study was approved by our medical ethics and human research committee. Written informed consent was obtained from each patient before enrollment.

In all cases, lidocaine 2.5% and prilocaine 2.5% (eutectic mixture of local anesthetic, AstraZeneca Pharmaceuticals LP, Wilmington, Del) cream was applied to the lesions 1 hour before treatment and Tegaderm (3M, St Paul, Minn) was used to occlude the area. Randomly, patients received treatment consisting of one session of QSAL (AlexLAZR, Candela Laser Corp, Wayland, Mass) (755 nm, 50 nanoseconds, 3-mm spot size, 6.5-7.5 J/cm^2) in one cheek and two sessions of Quantum SR IPL device (ESC Medical Systems Ltd, Yokneam, Israel)[14] (560-1200 nm, double mode, 3.2/6.0 milliseconds, intervals 40 milliseconds, 26-30 J/cm^2 for session one and 28-32 J/cm^2 for session two) with integrated contact cooling in the other cheek during a 4-week interval. The clinical end point was defined as the point of immediate whitening without bleeding and tissue splatter for QSAL, and darkening of pigmented lesions with mild perilesional erythema for IPL. Postoperatively, patients were given antibiotic ointment to apply topically on the laser side until the lesions healed, then followed with sunscreen to

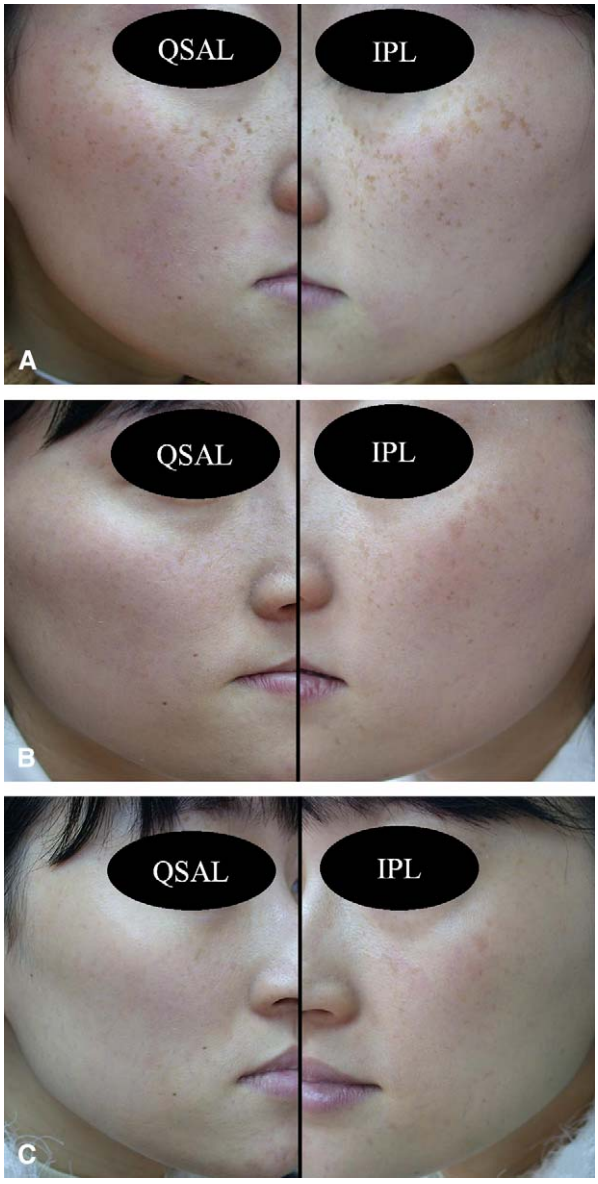

Fig 1. Standard digital photography of 28-year-old woman with freckles. **A**, Before treatment. **B**, After one session of Q-switched alexandrite laser (*QSAL*) and intense pulsed light (*IPL*) at week 4. **C**, After one session of QSAL and two sessions of IPL at week 12. Note greater improvement in side treated with QSAL.

prevent possible PIH and repigmentation. On the IPL side, only sunscreens were advised for postoperative care. Patients who developed PIH were treated with 4% hydroquinone cream to speed PIH resolution.

Clinical evaluations for the improvement in pigmentation were conducted at baseline and weeks 2, 4, 8, and 12. Digital photography documentation under the same condition (light source, room, and camera) was taken at baseline and at every visit. Any side effects, including hyperpigmentation and hypopigmentation, were also documented. Patients with unwanted pigmentary changes underwent additional follow-up at 6 months to ensure complete resolution. Patient photographs were reviewed by 3 independent physicians who were blinded to the study. To more accurately quantify the severity of pigmentation and any change during therapy, a pigmentation area and severity index (PSI) score was devised based on 3 parameters: the extent, the darkness, and the density of the pigmented lesions. This calculation was based on a similar scoring system, melasma area and severity index score devised for melasma.[15] Only a confined portion of one cheek was counted.

Area (the extent of pigmented lesions) was classified as: 0 = no involvement, 1 = less than 10% involvement, 2 = 10% to 29%, 3 = 30% to 49%, 4 = 50% to 69%, 5 = 70% to 89%, and 6 = 90% to 100% involvement of one cheek.

Darkness (the darkness of the pigmented lesions) was defined as: 0 = absent, 1 = slight, 2 = mild, 3 = marked, and 4 = severe.

Density (number of pigmented lesions per unit facial area) was calculated as: 0 = minimal, 1 = slight, 2 = mild, 3 = marked, and 4 = maximum.

These values were added to obtain the PSI score: PSI score (0-48) = (darkness + density) × area.

The improvement rate at the time of evaluation was defined as follows:

$$\text{Improvement rate at time of evaluation} = (\text{PSI}_{\text{pretreatment}} - \text{PSI}_{\text{posttreatment}})/\text{PSI}_{\text{pretreatment}} \times 100\%$$

The means of the scores recorded by the 3 physicians at baseline (pretreatment), week 4 (after one session of QSAL and IPL therapy), and week 12 (after one session of QSAL and two sessions of IPL therapy) were obtained to compare the efficacy of the treatments using Wilcoxon signed rank test. The risk factors associated with unwanted pigmentary changes were evaluated using Wilcoxon rank sum test for continuous variables and Fisher exact test for categorical variables. A P value of less than .05 was defined as statistically significant. All values were expressed as mean ± SD.

At the end of the study (week 12), all patients completed a questionnaire using a grading system to assess their subjective satisfaction with each treatment as follows: very satisfied, satisfied, slightly satisfied, and dissatisfied. Patients were also asked to select the treatment that achieved the better result in their opinion, the treatment that was more painful, and the treatment that they would choose if further treatments were needed.

Table II. Improvement in pigmentation area and severity index scores by treatments

	Freckles (n = 15)			Lentigines (n = 17)		
	QSAL	IPL	*P* value*	QSAL	IPL	*P* value*
Baseline						
PSI score, 0-48	13.2 ± 7.0	13.9 ± 6.5	.1	9.8 ± 5.7	9.5 ± 5.3	.9
Wk 4						
PSI score, 0-48	2.2 ± 1.6†	4.3 ± 2.5†	.002	4.8 ± 3.9†	4.1 ± 2.6†	.2
Improvement rate, %	81.0 ± 18.6	68.4 ± 16.1	.01	53.5 ± 18.8	56.0 ± 18.8	.4
Wk 12						
PSI score, 0-48	1.8 ± 1.2†	2.8 ± 1.7†	.01	3.9 ± 3.3†	3.4 ± 2.1†	.3
Improvement rate, %	85.5 ± 8.7	79.8 ± 8.7	.04	61.5 ± 17.1	61.9 ± 16.5	.4
Risk of PIH	1/15 (7%)	0/15 (0%)	.5	8/17 (47%)	0/17 (0%)	.001

IPL, Intense pulsed light; *PIH*, postinflammatory hyperpigmentation; *PSI*, pigmentation area and severity index; *QSAL*, Q-switched alexandrite laser.
*Difference between sides treated with QSAL and IPL.
†$P < .0001$ compared with baseline.

RESULTS

All 32 patients were women, age ranged from 26 to 57 years, with Fitzpatrick skin phototypes III (n = 11) or IV (n = 21). There was no significant difference in baseline severity of pigmentation between the sides receiving different treatments ($P > .05$). The characteristics of the patients are shown in Table I.

All patients completed the 12-week study. All obtained obvious improvement in PSI scores and all 3 component values after QSAL and IPL treatment ($P < .0001$ compared with baseline). In 15 patients with freckles, the improvement rates in PSI scores after one session of QSAL treatment was significantly higher than that after one session of IPL treatment at week 4 ($P = .01$) and two sessions of IPL treatment at week 12 ($P = .04$) (Fig 1). In 17 patients with lentigines, the improvement rates after both treatments were similar (Table II).

PIH was noted in 9 of 32 patients (28%) within 2 to 4 weeks after QSAL therapy, which completely resolved within 3 months in 3 patients and within 4 to 6 months in 6 patients. No one developed PIH after IPL therapy. More patients with lentigines developed PIH (8 of 17, 47%) than in those with freckles (1 of 15, 7%) ($P = .01$). The incidence of PIH caused by QSAL was significantly higher than hyperpigmentation associated with IPL in patients with lentigines ($P = .001$), but not in patients with freckles ($P > .05$). The occurrence of PIH did not correlate well with age or Fitzpatrick skin types. Hypopigmentation and prolonged erythema were not observed in any of the study patients (Table II).

For further analysis, patients with lentigines were subdivided into those who did or did not develop PIH after QSAL therapy. In patients with PIH, the improvement rates were significantly higher in the sides treated with IPL than QSAL at week 4 ($P = .04$) (Fig 2). Higher baseline PSI scores were noted in patients with PIH than those without PIH in the sides treated with QSAL ($P = .01$) (Table III).

Of the 15 patients with freckles, 12 patients (80%) thought QSAL provided better results than IPL and 11 patients (73%) preferred QSAL if further treatment was required. Of the 17 patients with lentigines, 8 patients (47%) preferred QSAL and 9 others (53%) preferred IPL if further treatment was required (Table IV).

DISCUSSION

This study was well designed to compare the efficacy and side effects of QSAL and IPL for freckle and lentigine treatment in Asian persons. Using either therapy in this study, all patients achieved obvious improvement. PIH was more frequently found after QSAL therapy in patients with lentigines. The QSAL provided quicker and more effective treatment than IPL in patients with freckles who had a low risk of PIH. In patients with lentigines, there was no difference in efficacy between QSAL and IPL. However, after subgroup analysis, IPL provided better therapeutic effect than QSAL in patients with PIH.

The QSAL selectively destroyed melanosome-containing cells while preserving surrounding tissues by following the principle of selective photothermolysis, which was required using a laser with a wavelength strongly absorbed by melanin (300-1200 nm) and a pulse duration shorter than the thermal relaxation time of melanosome (50-280 nanoseconds) in the treatment of pigmented disorders.[16-18] The IPL with 560- to 1200-nm wavelengths and 3.2- to 6.0-millisecond pulse durations (which were much longer than the thermal relaxation time of

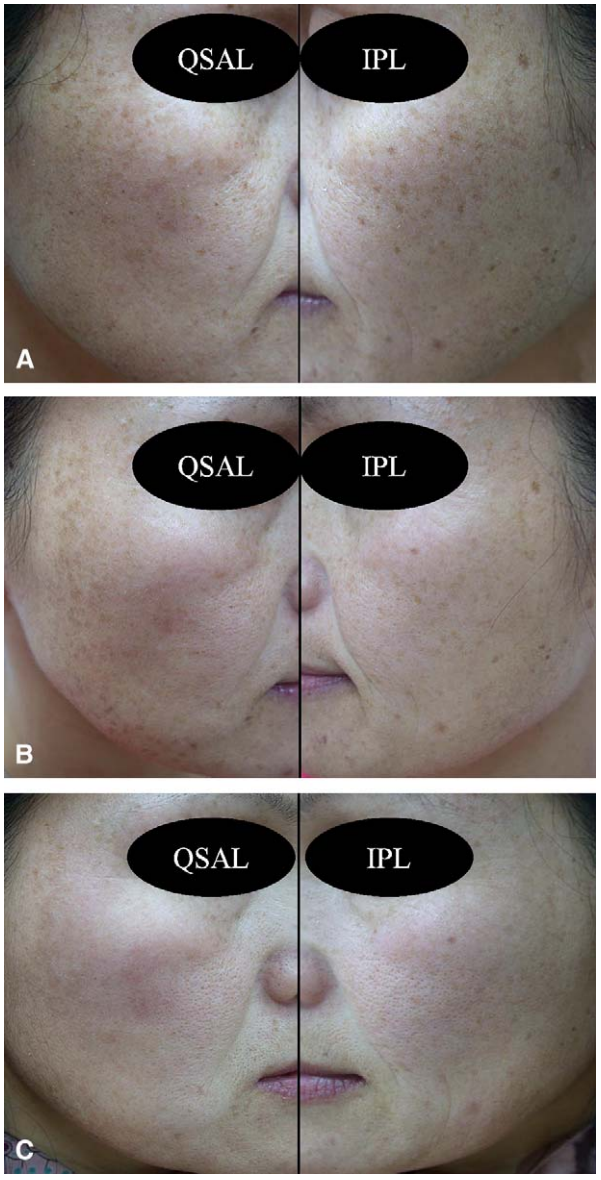

Fig 2. Standard digital photography of 45-year-old woman with lentigines. **A**, Before treatment. **B**, After one session of Q-switched alexandrite laser (*QSAL*) and intense pulsed light (*IPL*) at week 4. Note development of postinflammatory hyperpigmentation (PIH) in side treated with QSAL. **C**, After one session of QSAL and two sessions of IPL at week 12. Note partial resolution of PIH.

melanosome, but shorter than that of epidermis [10 milliseconds]) caused a gradual and diffuse epidermal necrosis while preserving the dermis. To prevent nonspecific epidermal injury, IPL should be used with a pulse intensity smaller than that of QS pigmented laser, together with a split pulse and cooling system.[14,19] These modifications may produce less effective results on pigmented lesions than the QS-pigmented laser. In this study, even one session of QSAL therapy was more effective than two sessions of IPL therapy in patients with freckles. More than 3 sessions of IPL might be required to obtain the same efficacy as one session of QSAL therapy.

The QSAL produced a higher risk of PIH than IPL especially in patients with lentigines in this study. QS pulse radiation generated acoustic waves by microvaporization and thermal expansion leading to photomechanical damage of pigmented cells and superficial vessels.[20] Inflammatory mediators then altered the activity of melanocytes and resulted in hyperpigmentation in persons with dark skin.[21] Among various QS pigmented lasers, the risk of PIH caused by QSAL might be the lowest because wavelengths between 600 and 900 nm (QSAL: 755 nm, QSRL: 694 nm) are preferentially absorption by melanin over oxyhemoglobin.[3,22] This resulted in a lesser degree of vascular damage than QS Nd:YAG laser (532 and 1064 nm), and the longer pulse duration (QSAL: 50-100 nanoseconds) produced less tissue fragmentation and splatter than QSRL (20-40 nanoseconds) and QS Nd:YAG laser (6-10 nanoseconds).[6,23,24] Like long pulse lasers, IPL did not have a photomechanical effect. Hence, the risk of pigmentary changes caused by IPL was much lower than that of QS lasers.[19,24] In addition, the microcrusts[19] formed by IPL during the healing process were cosmetically more acceptable than the macrocrusts formed by QS lasers. The lack of downtime associated with IPL treatment made multiple sessions acceptable.

In this study, the incidence of PIH caused by QSAL therapy was higher in patients with lentigines (47%) than in those with freckles (7%) even though similar fluences were used. Melanocytic hyperplasia in lentigines and the different genetic background between these two entities might explain this finding.[1,2] Jang et al[6] reported a 4% incidence of PIH for freckle treatment using QSAL with a parameter similar to this study in Korean persons. However, the incidence of PIH for lentigine treatment using QSAL had not been reported in the literature. Darker skin types are prone to laser-induced pigment alteration. However, there was no difference in the incidence of PIH between Fitzpatrick skin types III and IV in this study. The development of PIH in patients with lentigines was well correlated with baseline PSI scores, probably because of the existence of more active melanocytes in patients with more severe lentigines. Further studies with larger sample sizes are required to confirm this correlation. For lentigine treatment in Asian persons, IPL should be considered first. QS laser treatment should be initiated at lower fluences and gradually increased as necessary

Table III. Subgroup analysis in patients with lentigines who did or did not develop postinflammatory hyperpigmentation after Q-switched alexandrite laser therapy

	PIH (n = 8)			No PIH (n = 9)		
Age, y	46.2 ± 3.3			45.7 ± 7.4		
Skin types, III/IV	2/6			2/7		
Treatment modalities	**QSAL**	**IPL**	***P* value***	**QSAL**	**IPL**	***P* value***
Baseline						
PSI score, 0-48	13.3 ± 6.1	11.8 ± 6.5	.4	6.8 ± 3.3	7.5 ± 3.1	.5
Wk 4						
PSI score, 0-48	7.4 ± 4.3†	4.9 ± 3.1†	.03	2.4 ± 1.1†	3.4 ± 2.0†	.1
Improvement rate, %	43.2 ± 19.9	57.5 ± 17.9	.04	62.7 ± 12.5	54.6 ± 20.5	.1
Wk 12						
PSI score, 0-48	5.7 ± 4.1†	3.9 ± 2.7†	.03	2.2 ± 1.3†	2.9 ± 1.4†	.1
Improvement rate, %	56.7 ± 19.5	66.5 ± 12.6	.2	65.8 ± 14.5	57.8 ± 19.1	.1

IPL, Intense pulsed light; *PIH*, postinflammatory hyperpigmentation; *PSI*, pigmentation area and severity index; *QSAL*, Q-switched alexandrite laser.
*Difference between sides treated with QSAL and IPL.
†$P < .01$ compared with baseline.

Table IV. Patient survey results by treatments

	Freckles (n = 15)		Lentigines (n = 17)	
	QSAL	**IPL**	**QSAL**	**IPL**
Patient satisfaction				
Very satisfied	11	7	5	2
Satisfied	3	5	6	9
Slightly satisfied	1	2	5	6
Dissatisfied	0	1	1	0
Better result	12	3	8	9
More painful	14	1	16	1
Preferred treatment	11	4	8	9

IPL, Intense pulsed light; *QSAL*, Q-switched alexandrite laser.

because the risk of PIH increases with higher fluences used.[3] For the treatment of PIH, daily use of broad-spectrum sunscreens is essential. Many topical medications including hydroquinone, retinoids, kojic acid, and azelaic acid (either used individually or in combination), and chemical peels, have been used with satisfactory results.[21]

A new scoring system based on the area, darkness, and density of the pigmented lesions was developed to quantify the severity of and change in pigmentation. The component values could be studied separately and together as an overall score. The PSI score only counted a confined portion of a cheek because of the split-face design in this study. The forehead and the chin were not evaluated because most of the pigmented lesions were confined to the cheeks in our patients.

In conclusion, both QSAL and IPL were effective in the treatment of freckles and lentigines in Asian persons although the risk of PIH caused by QSAL was high in patients with lentigines. The QSAL was superior to IPL in the treatment of freckles. However, IPL should be considered first in the treatment of lentigines and in patients who did not want to have downtime. We recognized the limitations of this study with its small sample size and short follow-up period. Further studies with a larger sample size, long-term follow-up, and comparison of different equipment are needed to establish the optimal treatment modalities for pigmented disorders in Asian skin.

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