A split-face, single-blinded, randomized controlled comparison of alexandrite 755-nm picosecond laser versus alexandrite 755-nm nanosecond laser in the treatment of acquired bilateral nevus of Ota–like macules

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Background: Q-switched alexandrite lasers (QSALs) have been used for the treatment of acquired bilateral nevus of Ota–like macules (ABNOMs). Currently, picosecond alexandrite laser (PSAL) pulses have become available for pigmentary disorders. However, no studies have compared PSAL and QSAL in the treatment of ABNOM.

Objective: We sought to compare the efficacy and safety of PSAL and QSAL in the treatment of ABNOM.

Methods: Each patient (n = 30) received 3 treatments at 6-month intervals. Matching areas were delimitated on the face of each patient (left/right comparison); 1 side was treated with PSAL and the other side was treated with QSAL. The safety and efficacy of the 2 lasers were determined by visual assessment and self-report from patients 6 months after the final treatment.

Results: The PSAL-treated area achieved significantly better clearance (3.73 vs 2.4) with less severe pain (4.47 vs 5.16). The incidence rate of postinflammatory hyperpigmentation was 27.77% and 54.44% for the PSAL and QSAL treatments, respectively, and the duration of postinflammatory hyperpigmentation was 1.32 and 1.74 months, respectively ($P < .001$).

Limitations: The limitations of our study include the small sample size and the lack of objective evaluation.

Conclusion: Compared with QSAL, PSAL therapy afforded significantly better clinical outcomes and fewer side effects in the treatment of ABNOM. (J Am Acad Dermatol 2018;79:479-86.)

Key words: acquired bilateral nevus of Ota–like macules; photomechanical effect; picosecond alexandrite laser; postinflammatory hyperpigmentation; Q-switched alexandrite laser.

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INTRODUCTION

Acquired bilateral nevus of Ota–like macules (ABNOMs) or Hori nevus was first described by Hori et al[1] in 1984. Unlike the nevus of Ota, melanocytes in the ABNOM are mostly distributed in the papillary dermis and contain melanosomes in the earlier stages of melanization (stages II-IV).[2,3] ABNOMs are a common dermal pigmentation disorder and are predominantly observed in middle-aged women in eastern Asia. In an investigation conducted in Shanghai of 8680 patients ranging in age from newborns to 99 years old, the prevalence of ABNOM was 2.5% (0.5% males and 4.2% females).[4] Alongside ABNOM, most pigmentary disorders are histologically associated with increased deposition of melanosomes in the epidermis or dermis. Melanosomes have a larger particle size than tattoo pigments, and therefore have a longer thermal relaxation time (50-250 ns).[5] At present, Q-switched lasers (ruby, alexandrite, and neodymium-doped yttrium aluminium garnet), operating in nanoseconds (5-100 ns), are the lasers of choice for the treatment of pigmentary disorders.[6-11] Compared to the Q-switched ruby laser, the Q-switched alexandrite laser (QSAL) has a longer wavelength that is suitable for deeper skin penetration[12] and is frequently used for treating pigmented lesions, including ABNOMs.[10,11,13] However, when using QSAL, multiple sequential treatments are needed to achieve the desired improvement. Certain side effects, especially postinflammatory hyperpigmentation (PIH) after QS laser treatments, are particularly common in patients of Asian descent.[13,14]

Picosecond alexandrite laser (PSAL; Cynosure, Westford, MA), which was first approved in 2012 by the US Food and Drug Administration, is extensively used for the removal of unwanted tattoos and for the treatment of pigmented lesions in all skin types.[15] A pulse duration in the subnanosecond range (10^{-12} s) is supposed to be better than a pulse duration in the nanosecond range (10^{-9} s) when removing unwanted tattoo pigments because of the generation of higher peak temperatures and better heat confinement.[16-18] Because the PSAL can emit even shorter picosecond energy pulses when targeting pigmented chromophores, laser treatments have the advantage of creating a greater photomechanical effect, with less unwanted heat diffusion into surrounding structures.[19]

Nevertheless, to date, no prospective comparative study has examined a nanosecond laser (NSL) versus a picosecond laser (PSL) for the treatment of ABNOMs. This is, to our knowledge, the first prospective, split-face, self-controlled comparative study that evaluates the efficacy and safety of these 2 lasers in the treatment of ABNOMs (Chinese Clinical Trial Register ChiCTR-ONh-17012114).

CAPSULE SUMMARY

- Q-switched alexandrite lasers have been used for treating of acquired bilateral nevus of Ota–like macules.
- Picosecond alexandrite laser treatment achieved better clearance (3.73 vs 2.4) with a lower incidence of postinflammatory hyperpigmentation (27.77% vs 54.44%) compared with Q-switched alexandrite laser treatment.
- Picosecond alexandrite laser treatment afforded better clinical improvements and fewer side effects for patients with acquired bilateral nevus of Ota–like macules

METHODS

Subjects

This is a prospective randomized, split-face, self-controlled comparative study designed to evaluate the safety and effectiveness of PSAL versus QSAL in the treatment of ABNOM. The study was conducted in the Department of Laser and Aesthetic Medicine, Shanghai Ninth People's Hospital, over a 20-month period (October 2015 to June 2017). The exclusion criteria were as follows: increased sensitivity to light, scars or florid inflammation of the pigmented skin or area immediately surrounding it, pregnancy, and unrealistic patient expectations. Patients who had used bleaching agents and those who had received any treatment for pigmentation within 1 year of enrollment were also excluded. The clinical diagnosis of ABNOM was based on examination of the patient's history. A 365-nm Wood's lamp was occasionally used when the diagnosis was uncertain. Patients diagnosed with the coexistence of other pigmented lesions were not enrolled. Age, sex, and Fitzpatrick skin type were recorded for each patient. Fitzpatrick skin type was based on answers to a sun-exposure reaction questionnaire, from the investigator's objective determination, or from photographic reviews. Photographs were taken before the initial laser treatment and at follow-up visits. Before the first treatment, patients were given verbal and written information about the course of the study, potential complications, and therapeutic alternatives.

This study was approved by the Institutional Review Board of Shanghai Ninth People's Hospital, China. All patients provided appropriate written and verbal informed consent.

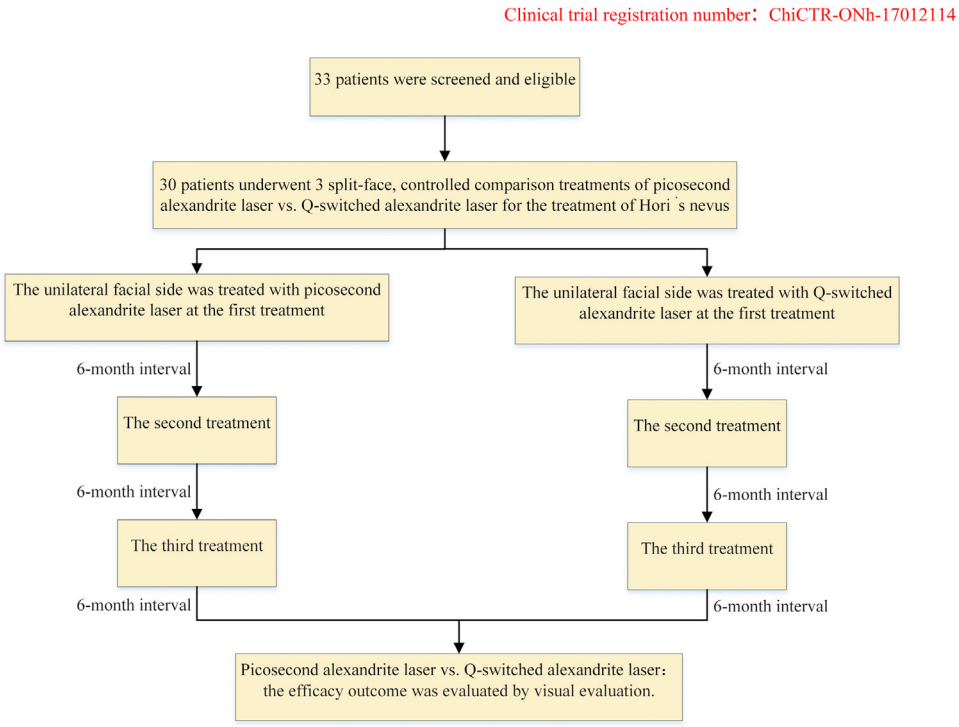

Fig 1. Patient enrollment and treatment randomization.

Table I. Quartile improvement scale

	No. of patients (%)	
Quartile improvement scale	**PSAL**	**QSAL**
0 = No improvement	0 (0)	0 (0)
1 = Poor (1-25%)	0 (0)	5 (16.7)
2 = Fair (26-50%)	1 (3.3)	11 (36.7)
3 = Good (51-75%)	6 (20.0)	11 (36.7)
4 = Excellent (76-100%)	23 (76.7)	3 (10.0)
P value	< .001	

PSAL, Picosecond alexandrite laser; *QSAL*, Q-switched alexandrite laser.

Table II. Likert satisfaction scale

	No. of patients (%)	
Likert satisfaction scale	**PSAL**	**QSAL**
1 = Very dissatisfied	0 (0)	0 (0)
2 = Dissatisfied	0 (0)	2 (6.7)
3 = Slightly satisfied	2 (6.7)	16 (53.3)
4 = Satisfied	5 (16.7)	7 (23.3)
5 = Very satisfied	23 (76.7)	5 (16.7)
P value	< .001	

PSAL, Picosecond alexandrite laser; *QSAL*, Q-switched alexandrite laser.

Laser therapy

All subjects underwent 3 treatments at an interval of 6 months because previous publications have shown that good to excellent results for ABNOM can be attained after 2 to 11 sessions with NSLs.[10] An interval of 6 months was chosen as a resting period to allow for complete recovery between laser treatments.[14]

Split-face areas were delimited on each patient; 1 side was treated with a 755-nm PSAL (Picosure; Cynosure, Westford, MA) at 750 picoseconds, and the other was treated with a 755-nm QSAL (Accolade; Cynosure) at 70 nanoseconds. Left and right delimited areas were randomly allocated to 1 of the 2 laser devices. Randomization was conducted by employees who were not otherwise involved in the trial. Random sequence software (available at: http://www.dxy.cn/bbs/topic/21117904) produced a randomized number sequence, 1-xx, which was assigned to each patient. Patients given odd numbers were treated with PSAL on the left side of the face, while patients with even numbers were treated on their left side with QSAL (Chinese Clinical Trial Register ChiCTR-ONh-17012114; Fig 1).

Test spots were used to determine threshold fluences on each patient and define treatment endpoints (ie, the appearance of slight whitening, without bleeding and tissue splatter). The treatment parameters for PSAL were 2- to 2.5-mm spot size, 4.07 to 6.37 J/cm^2 fluence, 2.5 Hz speed, and single pass without overlapping; the treatment parameters for QSAL were 3-mm spot size, 6.0 to 8.0 J/cm^2 fluence, 2 Hz, and single pass without overlapping.

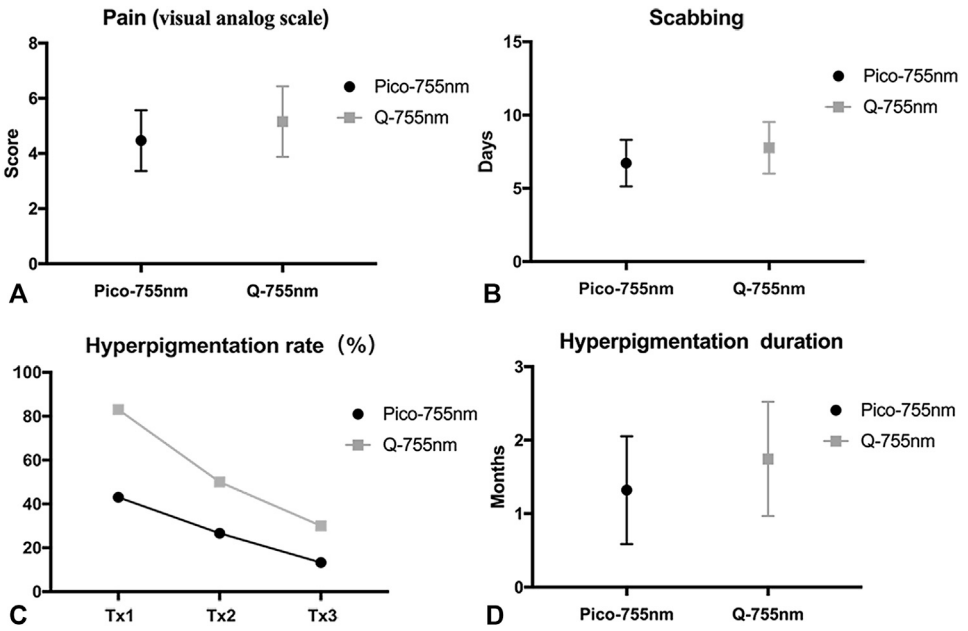

Fig 2. Split-face comparison of adverse events between the picosecond 755-nm laser (Pico-755nm and PSAL) and Q-switched 755-nm laser (Q-755nm and QSAL). **A**, Visual analog scale patient scores. Average pain sensation during treatments was reported as 4.47 (standard deviation [SD] = 1.104) and 5.16 (SD = 1.280) for the facial sides receiving PSAL and QSAL, respectively ($P < .001$). **B**, Average duration of scabbing. Scabbing was reported for a mean of 6.72 (SD = 1.587) days in the PSAL group and 7.77 (SD = 1.761) days in the QSAL group ($P < .001$). **C**, Postinflammatory hyperpigmentation (PIH) rates after 3 treatments. The rates were significantly lower when using PSAL compared to QSAL (27.77% vs 54.44%, $P < .001$). **D**, Average duration of PIH. The duration of PIH was 1.32 months (SD = 0.73) for the PSAL-treated sides and 1.74 months (SD = 0.77) for the QSAL-treated sides ($P = .009$).

Appropriate eye protection was worn while the laser was in use, and treated areas were subsequently cooled with cold packs for 30 minutes. Patients were instructed to apply a topical antibiotic ointment after the procedure until the lesions healed, followed by regular (at least every 2 hours) application of sunscreen with a minimum sun protection factor of 30. Additional topical ointments for depigmentation, such as hydroquinone or tretinoin, were not used in our study.

Evaluation

All patients were photographed using standard digital photography (Nikon D90; Nikon, Tokyo, Japan) and identical lighting conditions pretreatment, at follow-up visits, and 6 months after the final treatment.

The quartile improvement scale was used to assess clearance in the treated areas 6 months after the final treatment: no improvement (0%, score 0), poor (1-25%, score 1), fair (26-50%, score 2), good (51-75%, score 3), or excellent (76-100%, score 4).[20] ABNOM lesions were assessed by 2 experienced dermatologists in a fully blinded manner (ie, no knowledge about the laser treatment settings or outcomes). When different improvement scores were reported for a given lesion, a mean score was calculated.

At the end of the study, patients documented their degree of satisfaction using a Likert satisfaction scale, which was recorded as very satisfied (5), satisfied (4), slightly satisfied (3), dissatisfied (2), or very dissatisfied (1).[20]

Topical anesthetics were not used pretreatment, and subjects were asked to indicate the degree of pain immediately after the session using a visual analog scale ranging from 0 (no pain at all) to 10 (unbearable pain).

ABNOM lesions were assessed pretreatment, immediately after every treatment, and 6 months after final treatment. Transient and permanent adverse effects (eg, blistering, crusting, swelling, bleeding, hypo- and hyperpigmentation, and scars) were evaluated weekly throughout the first 3 months after each treatment by 2 investigators who were blinded to the allocation of the treatments. Questions were asked about side effects through phone calls, and self-portraits were provided by the patients via email for confirmation.

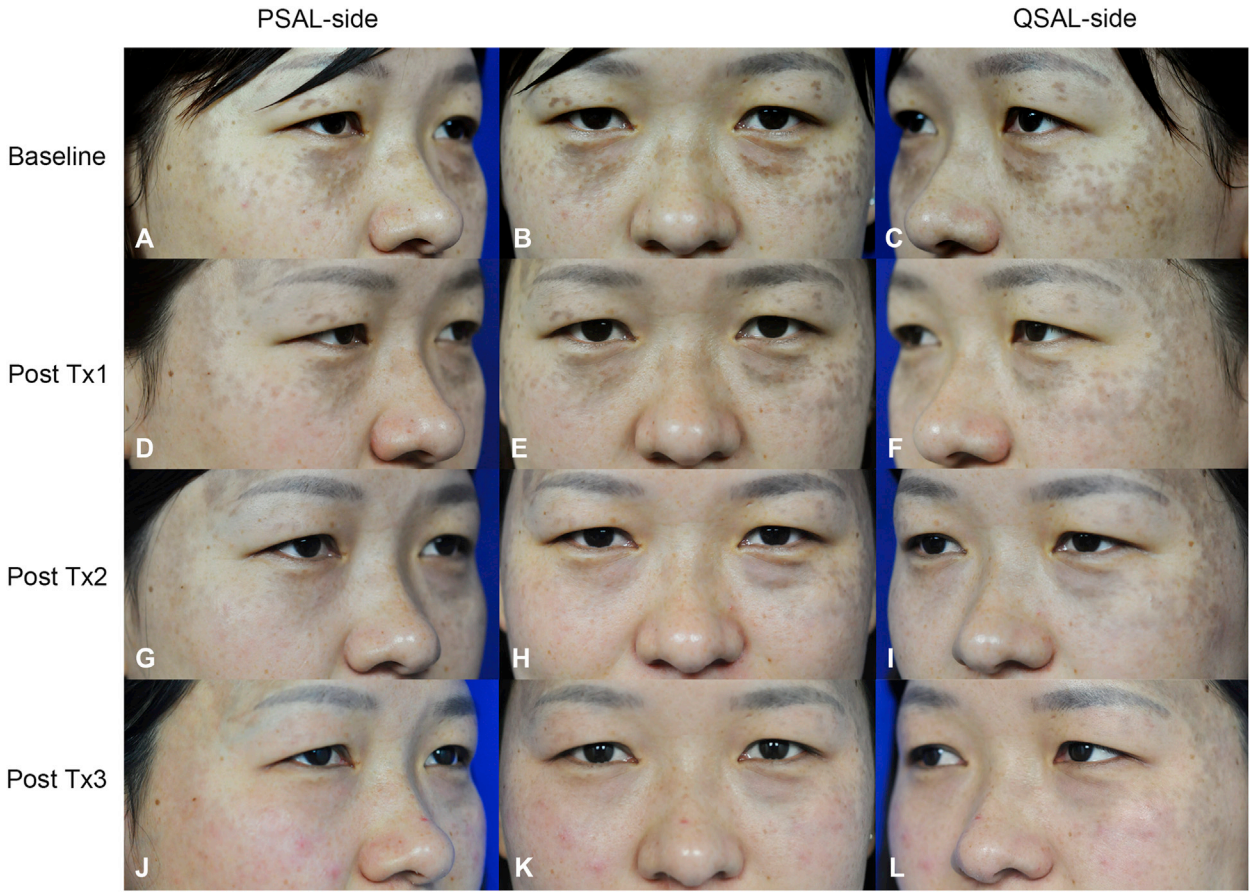

Fig 3. Female, 24 years old. Bilateral acquired bilateral nevus of Ota–like macule lesions were randomly selected for treatment with picosecond alexandrite laser (PSAL) or Q-switched alexandrite laser (QSAL). **A-C**, Before treatment. **D-F**, Six months after the first laser treatment. **G-I**, Six months after the second laser treatment. **J-L**, Six months after the third laser treatment. Note that the sides treated with PSAL showed significantly more improvement than the sides treated with QSAL.

Data analysis

All data gathered were analyzed using SPSS software (version 20.0; IBM, Armonk, NY) and GraphPad Prism 7 software (GraphPad Software, Inc., San Diego, CA). A Wilcoxon test for 2-paired samples was used to compare improvement and transient side effects between the 2 devices, the rates of PIH were compared using the χ^2 test, and the duration of PIH was compared with Mann–Whitney tests. $P < .05$ was considered statistically significant.

To determine the appropriate sample size, we wanted to test the null hypothesis that there was ≤10% difference in clearance between the 2 lasers. With a patient population of 30, a 30% difference between the 2 lasers would refute this hypothesis with a power of 80%. With an estimated 10% rate of lost follow-up, a total of 33 patients was deemed adequate for the study.

RESULTS

Of the 33 patients enrolled in this study, 30 patients (5 male and 25 female) finished all 3 laser treatments. Patient age ranged from 18 to 50 years (mean age, 30 years). Fitzpatrick skin type III was observed in 7 patients (23%), whereas 23 patients (77%) had Fitzpatrick skin type IV.

Efficacy outcome

Each patient received a total of 3 treatments at 6-month intervals. The average scores of the quartile improvement scale were 3.73 (standard deviation [SD] = 0.521) and 2.4 (SD = 0.894) after the final treatment for the PSAL group and QSAL group, respectively ($P < .001$). In all, 23 (76.7%) and 6 (20.0%) patients were assessed as excellent and good improvement, respectively, for the PSAL-treated sides, whereas only 3 (10%) and 11 (36.7%) patients

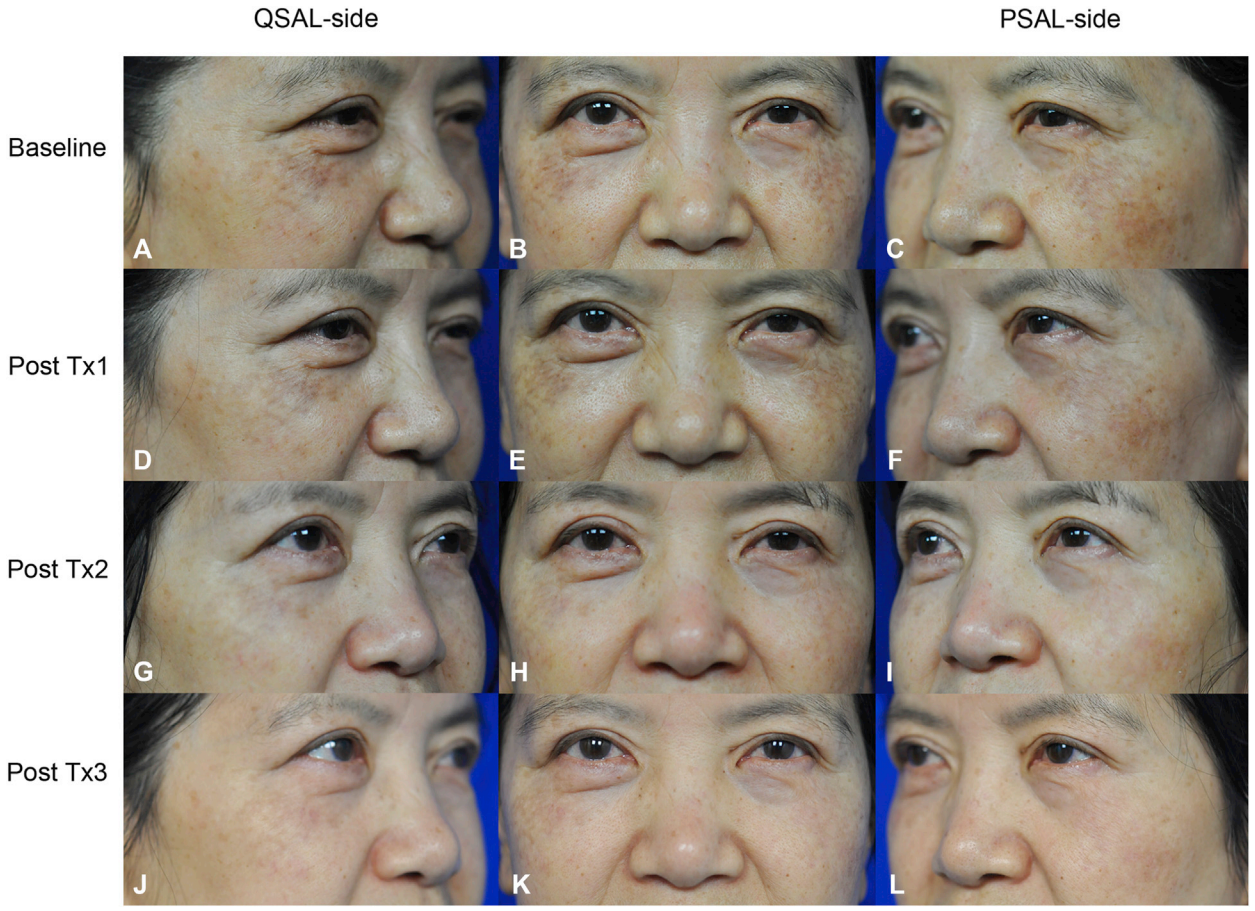

Fig 4. Female, 51 years old. Bilateral acquired bilateral nevus of Ota–like macule lesions were randomly selected for treatment with picosecond alexandrite laser (PSAL) or Q-switched alexandrite laser (QSAL). **A-C**, Before treatment. **D-F**, Six months after the first laser treatment. **G-I**, Six months after the second laser treatment. **J-L**, Six months after the third laser treatment. Note that the sides treated with PSAL showed significantly more improvement than the sides treated with QSAL.

showed the same rates of improvement for the QSAL-treated sides (Table I).

Satisfaction rates were based on self-reported improvement by the patients 6 months after the final treatment. The average scores (1-5 scale) were 4.7 (SD = 0.596) and 3.5 (SD = 0.861) for the areas receiving PSAL and QSAL, respectively ($P < .001$). Overall, 28 patients (93.4%) reported "satisfied" to "very satisfied" for the PSAL-treated sides, while only 12 patients (40.0%) reported the same degree of satisfaction for the QSAL-treated lesions. The results reported by the blinded evaluators and by the patients indicate that the 755-nm alexandrite laser with picosecond pulse was significantly more effective than the laser with nanosecond pulse (Table II).

Adverse events

Average pain sensation during treatments was reported at 4.47 (SD = 1.104) and 5.16 (SD = 1.280) for the areas receiving PSAL and QSAL, respectively ($P < .001$; Fig 2, *A*). Scabbing was reported for a mean of 6.72 (SD = 1.587) days in PSAL-treated lesions and 7.77 (SD = 1.761) days in areas receiving QSAL ($P < .001$; Fig 2, *B*). However, no significant difference was observed among other transient side effects between the 2 laser treatments. All patients experienced mild erythema and mild edema on both sides after treatment, which resolved within 24 hours. Blistering occurred in 6.66% patients and 8.88% patients on the PSAL- and QSAL-treated sides, respectively, but resolved within 3 to 7 days posttreatment. Acneiform miliaris occurred in 2.22% of patients, on both sides, after treatments, and resolved in 10 days posttreatment. No patients experienced hyperkeratosis, scarring, or hypopigmentation.

PIH rates were significantly lower (27.77% vs 54.44%, $P < .001$) after treatments with PSAL

compared to QSAL. The duration of PIH was also much shorter for the PSAL-treated sides, with a mean of 1.32 (SD = 0.73) months, compared to 1.74 (SD = 0.77) months reported for the QSAL-treated sides (P = .009; Fig 2, *C* and *D*).

Figs 3 and 4 show improvements in the appearance of ABNOMs after every treatment compared to the baseline. The side treated with PSAL showed more improvement than the side treated with QSAL.

DISCUSSION

In this randomized, split-face, self-controlled comparative study, the efficacy of PSAL and QSAL in the treatment of ABNOMs was evaluated. After all patients underwent 3 treatment sessions (PSAL on one side of the face and QSAL on the other), the ABNOM lesions were evaluated and it was observed that PSAL-treated sides experienced significantly better clearance, which may be explained by the shorter pulse duration (750 picoseconds vs 70 nanoseconds). When targeting pigmented chromophores, laser energy emitted by PSLs in the shorter picosecond domains is thought to generate a greater photomechanical effect, with tensile strength that exceeds the tissue's ultimate tensile stress, leading to tissue fracture and ablation.[21] Theoretically, the additional photomechanical effect produced by the shorter pulse duration would translate into superior clinical efficacy compared to QSALs. The lower fluence PSAL used may also account for the shorter recovery time and less discomfort.[22] The transient side effects, including pain sensation and scabbing, were also significantly lower on the PSAL-treated sides compared to QSAL.

Previous studies using QSLs for the treatment of pigmented lesions in Asians have highlighted a major concern of PIH. Moreover, laser treatments for ABNOM using nanosecond pulses are often associated with significantly higher rates of PIH compared to other benign pigmented lesions, such as nevus of Ota and lentigo, with reported rates of 75% to 87%.[10,13] The higher presence of perivascular melanocytes in ABNOM is considered responsible for PIH. The indirect vascular damage caused by nanosecond laser irradiation could induce inflammatory changes and melanogenesis.[23] We suppose that since the pulse duration of the PSAL is far shorter than the thermal relaxation time of melanosomes, the laser energy absorbed is confined within the target chromophores, which results in minimal disruption to surrounding structures and vasculature.[19] However, studies comprising histologic investigations are needed to better determine the exact postlaser changes associated with the 2 devices.

Conclusive evidence is already available for the clinical superiority of picosecond devices in tattoo removal[16-18] and in the treatment of certain pigmented lesions.[24,25] However, these studies were conducted retrospectively, without a control arm. To the best of our knowledge, our study is the first prospective study to prove the superior efficacy of PSAL compared to QSAL in treating ABNOMs. Limitations of this study include its small sample size and subjective evaluation. Further studies with objective assessments are necessary to validate our findings.

In conclusion, the PSAL afforded more favorable responses, a shorter recovery time, less pain, and fewer side effects in the treatment of ABNOMs than the QSAL. The use of lower energy resulted in fewer posttreatment reactions and easier posttreatment wound care.

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