ORIGINAL ARTICLE

Comparison of a picosecond alexandrite laser versus a Q-switched alexandrite laser for the treatment of nevus of Ota: A randomized, split-lesion, controlled trial

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Background: Novel picosecond lasers have been available for various pigmentary disorders. However, there are limited data directly comparing picosecond lasers and Q-switched lasers for treatment of nevus of Ota.

Objective: To compare the efficacy and safety of a picosecond alexandrite laser (PSAL) with a Q-switched alexandrite laser (QSAL) for the treatment of nevus of Ota.

Methods: Each lesion of 56 enrolled participants was split into 2 parts and randomly assigned to either the PSAL or QSAL treatment arm. Each lesion was treated in up to 6 sessions in 12-week intervals. Efficacy and safety were determined using blinded visual evaluation and self-report at each follow-up visit.

Results: The PSAL arm achieved a significantly better clearance (5-point scale, PSAL 4.53 vs QSAL 4.0) with fewer sessions (PSAL 5.26 vs QSAL 5.87) and less severe pain (Visual Analog Scale, PSAL 5.61 vs QSAL 6.40). Patients were more satisfied with PSAL than QSAL (Likert scale, 4.5 vs 4.0). Occurrences of postinflammatory hyperpigmentation (PSAL 26% vs QSAL 34%) and hypopigmentation (PSAL 21% vs QSAL 47%) were also lower in PSAL than QSAL arm.

Limitations: Lack of objective assessments and outcome measures.

Conclusion: PSAL demonstrated better clinical results and fewer adverse events than QSAL for the treatment of nevus of Ota. (J Am Acad Dermatol https://doi.org/10.1016/j.jaad.2019.03.016.)

Key words: nevus of Ota; photomechanical effect; picosecond alexandrite laser; postinflammatory hypopigmentation; Q-switched alexandrite laser; split-lesion.

Nevus of Ota is a benign dermal melanocytic nevus originally described by Ota and Tanino in 1939.[1] It usually presents as unilateral or occasionally bilateral, brown-to-bluish hyperpigmented macules and patches typically scattered along the first (ophthalmic) and second (maxillary) branches of the trigeminal nerve on the face. On histologic examination, pigmented, elongated dendritic melanocytes are distributed within the papillary dermis and upper reticular dermis, giving a distinctive discolored appearance.[2] Nevus of Ota is common among Asian populations with a varying prevalence of 0.02%-0.8%, and women are more often affected than men.[3,4]

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Despite its benign nature, nevus of Ota is associated with significant emotional and psychosocial stress brought about by its cosmetic disfigurement. Thus, proper management of facial lesions is crucial for the mental and social well-being of these patients. Treatment of nevus of Ota used to be challenging. Previous modalities, eg, cryotherapy and dermabrasion, were either ineffective or likely to cause unacceptable scarring or dyspigmentation.[5-7] Fortunately, over the past 2 decades, the advent of Q-switched lasers has revolutionized the way nevus of Ota is managed. Because of selective photothermolysis, Q-switched lasers are able to produce extremely brief, nanosecond pulse energy to specifically target the cutaneous pigment-laden melanocytes while significantly reducing collateral skin damage.[8] The efficacy and safety profiles of a variety of Q-switched lasers, primarily Q-switched ruby laser, Q-switched alexandrite laser (QSAL), and Q-switched neodymium-doped yttrium aluminum garnet laser, have been demonstrated.[9] Currently, they are the choice of treatment for most nevus of Ota patients. Nevertheless, multiple treatment sessions are often required, and postlaser complications are not uncommon.

CAPSULE SUMMARY

- There are limited data directly comparing picosecond lasers and Q-switched lasers for treating nevus of Ota.
- Picosecond alexandrite laser treatment achieved a better clearance with fewer sessions and lower incidences of postinflammatory dyspigmentation, demonstrating better clinical outcomes and fewer adverse events compared with Q-switched alexandrite laser.

Picosecond lasers represent a novel group of laser devices characterized by ultrashort, picosecond pulse duration. Compared with nanosecond lasers, picosecond lasers exert a greater photomechanical effect, presumably leading to an enhanced breaking down of small pigment particles.[10,11] A 755-nm picosecond alexandrite laser (PSAL) was first cleared in 2012 by US Food and Drug Administration for the removal of unwanted tattoo pigment. Recent studies show that PSAL is also effective for various other benign pigmentary disorders.[12-19] However, a direct comparison between a picosecond laser and a nanosecond laser therapy for nevus of Ota is lacking. The present study thus was conducted to compare the efficacy and safety of these 2 lasers for the treatment of nevus of Ota.

METHODS

Study design

This was a prospective, randomized, evaluator-blinded, split-lesion controlled, 2-arm trial conducted in accordance with the Declaration of Helsinki. The study was approved by the institutional review board of the Institute of Dermatology, Peking Union Medical College and Chinese Academy of Medical Sciences. All patients with nevus of Ota enrolled in the study provided written informed consent before inclusion. After enrollment, each lesion of included patients was divided into 2 marked parts, which were randomly assigned to be treated with either PSAL or QSAL according to a block randomization schedule generated by Statistical Analysis Software. Allocation concealment was preserved by using sequentially numbered, sealed envelopes. Patients received up to 6 treatment sessions at 12-week intervals and were followed up for 3 months after their final session. Efficacy and safety of the treatments were evaluated at each visit by using standard digital photographs. Lesions that were assessed as clinically clear underwent no further treatment.

Patient selection

Participants were recruited among the outpatients visiting the Department of Cosmetic Laser Surgery of the Institute of Dermatology, Peking Union Medical College and Chinese Academy of Medical Sciences. The diagnosis of nevus of Ota for prospective patients was established clinically by 3 investigators on the basis of lesion morphology, distribution, and history. Other inclusion criteria included being an adult (18-65 years old), having a Fitzpatrick skin type of III-V, and willingness to collaborate. Exclusion criteria included a history of previous treatments for nevus of Ota, scars, active infection, skin tumors or other conditions within or around the lesion, increased light sensitivity, immunodeficiency, a history of oral retinoids or excessive ultraviolet light exposure within the past 6 months, a history of hypertrophic scar or keloid, and known contact allergy to topical anesthetics containing lidocaine or prilocaine. Patients who participated in other clinical trials within the past 30 days or had severe systemic or psychiatric disorders were also excluded. Pregnant or lactating women were excluded as well. Before initial treatment, written informed consent was obtained from all patients. Baseline demographic data of patients, such as age, sex, age of onset, and Fitzpatrick skin type, were documented, and lesions were characterized in terms of color,[20] Tanino

Abbreviations used:

PIH: postinflammatory hyperpigmentation
PIHo: postinflammatory hypopigmentation
PSAL: picosecond alexandrite laser
QSAL: Q-switched alexandrite laser
SD: standard deviation

classification,[21] and Peking Union Medical College Hospital classification.[22]

Laser treatments

Before initial treatment, each patient's lesion was split-into 2 approximately equal, distinguishable parts and were randomly allocated to undergo either a 755-nm, 750-ps PSAL (Picosure; Cynosure, Westford, MA) or a 755-nm, 70-ns QSAL (Accolade; Cynosure) treatment. Before each session, each lesion was gently cleansed and marked. A compound anesthetic cream containing lidocaine 2.5% and prilocaine 2.5% (Tsinghua Unisplendour Pharmaceutical, Beijing, China) was then applied on the whole lesion under occlusion for an hour. After cleaning the topical anesthetic, test spots were used for each individual lesion to determine the threshold fluences. Moderate dermal whitening without obvious bleeding or tissue splatter was defined as the therapeutic endpoint for the PSAL arm. For the QSAL arm, intense dermal whitening was achieved. The parameters for the PSAL arm were 2.0−4.0-mm spot size, 1.59−6.37-J/cm^2 fluence, and 5-Hz frequency, and the parameters for the QSAL arm were 3.0-mm spot size, 5.0−7.0-J/cm^2 fluence, and 5-Hz frequency. For both arms, a single-pass method was used to minimize pulse stacking. Proper eye protection was always used during the procedure.

After the treatment, an antibiotic cream (Fucidin; LEO Pharma, Ballerup, Denmark) was immediately applied on the treated areas and subsequently cooled by cold packs for 30-60 minutes. Patients were instructed to apply the cream twice a day until the lesions healed. Ultraviolet light protection and sunscreens were also advised. For those who developed postinflammatory hyperpigmentation (PIH), hydroquinone 3% cream or arbutin 3% cream was used to accelerate its resolution.

Efficacy and safety evaluation

Standard digital photographs of the lesions were taken under consistent lighting conditions by using the VISIA camera system (Canfield Scientific, Parsippany, NJ) before initial treatment and at each follow-up visit.

The digital images were used by 3 independent, experienced dermatologists to blindly assess clinical efficacy. The primary efficacy outcomes were evaluated at baseline and each follow-up visit by using a 5-point scale with scores based on the percentage of pigment clearance: complete (95%-100%, score 5), excellent (75%-94%, score 4), good (50%-74%, score 3), fair (25%-49%, score 2), and poor (0%-24%, score 1). When different scores were generated for different lesions of the same patient, a mean score was adopted. Lesions scored 5 were considered to be clinically cleared and received no more treatment. At their final follow-up visits, patients were invited to report their degree of satisfaction with the 2 lasers on a 5-point Likert scale: very dissatisfied (1), dissatisfied (2), neither (3), satisfied (4), and very satisfied (5).

After each session, patients were asked to rate the degree of pain during PSAL and QSAL treatments, respectively, on a Visual Analog Scale ranging from 0 (no pain) to 10 (worst pain ever). Transient and permanent adverse effects associated with laser treatments, such as swelling, scabbing, blistering, bleeding, PIH, postinflammatory hypopigmentation (PIHo), scarring, and textural changes were documented by patients according to written instructions and verified at follow-up visits.

Statistical analysis

To determine the appropriate sample size, a null hypothesis was tested that there was no more than a 10% difference in lesion clearance between PSAL and QSAL arms. With a study population of 46, a 30% difference between the 2 lasers would refute this hypothesis with a power of 0.95. Assuming a dropout rate of 20%, a sample size of 56 patients (56 in each arm as a split-lesion 1-to-1 ratio design was adopted) was deemed adequate for the study.

Data analysis were performed with SPSS package (version 19.0; IBM-SPSS Inc, Armonk, NY) and GraphPad Prism 7 (GraphPad Software, San Diego, CA). Numeric variables were summarized as mean (standard deviation [SD]), and categorical variables were summarized as the counts and relative frequencies. Wilcoxon signed-rank test and Freidman exact test were used to compare the efficacy outcome parameters between the 2 lasers. For parameters associated with adverse events, the chi-squared, Wilcoxon signed-rank, and paired *t* tests were used. Statistical significance was defined as $P < .05$.

RESULTS

The trial was conducted during March 2016 and March 2018 in Nanjing, China. A total of 56 patients

Table I. Lesion characteristics of the patients enrolled in the study

Lesion characteristic	Patients, n/total (%)
Color	
Brown	14/56 (25)
Brown-violet	29/56 (52)
Violet-blue	13/56 (23)
Blue-green	0/56 (0)
Tanino classification	
Ia	1/56 (2)
Ib	8/56 (14)
Ic	2/56 (4)
II	7/56 (13)
III	14/56 (25)
IV	1/56 (2)
NA	23/56 (40)
PUMCH classification	
Ia1-a2	3/56 (5)
Ib1-b3	8/56 (14)
Ic	4/56 (7)
IIa1-a3	7/56 (13)
IIb	13/56 (24)
IIIa	9/56 (16)
IIIb	11/56 (19)
IV	1/56 (2)
V	0/56 (0)

NA, Not applied; *PUMCH*, Peking Union Medical College Hospital.

(112 lesions) were initially screened and enrolled, and 53 (16 male and 37 female) patients finally completed the study. Three patients (with 3 lesions in each arm) were lost to follow-up. The mean age of patients was 31.3 (range 18-54) years, and the average disease duration was 22.4 years. Fitzpatrick skin type III and IV were observed in 14% (8/56) and 86% (48/56) of the patients, respectively. No patient with Fitzpatrick skin type V was enrolled in this study. Lesion characteristics are summarized in Table I.

Efficacy outcomes

After an average of 5.26 (SD 1.0) treatment sessions, the PSAL arm achieved a mean efficacy score of 4.53 (SD 0.5); for the QSAL arm, after an average of 5.87 (SD 0.52) treatment sessions, the mean efficacy score was 4.0 (SD 0.71) ($P < .001$). At the final follow-up visits, 53% (28/53) of the lesions in the PSAL arm were assessed as complete clearance (score 5) and 47% (25/53) as excellent clearance (score 4). In comparison, 21% (11/53) of the lesions in the QSAL arm had complete clearance and 62% (33/53) had excellent clearance (Table II). Fig 1 shows a representative case before and after laser treatments.

For both the PSAL and QSAL arms, efficacy improved as the number of treatment sessions increased (Fig 2). In addition, PSAL demonstrated better outcomes than QSAL after each session.

Table II. Lesion clearance scores of different laser treatment arms

	Patients, n/total (%)	
Lesion clearance scale	PSAL	QSAL
5, complete, 95%-100%	28/53 (53)	11/53 (21)
4, excellent, 75%-94%	25/53 (47)	33/53 (62)
3, good, 50%-74%	0/53 (0)	7/53 (13)
2, fair, 25%-49%	0/53 (0)	2/53 (4)
1, poor, 0%-24%	0/53 (0)	0/53 (0)

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

Patients were generally more satisfied with the PSAL treatment. The mean satisfaction score for PSAL was 4.5 (SD 0.5) on the 5-point Likert scale, higher than the mean satisfaction score of 4.0 (SD 0.66) associated with the QSAL treatment ($P < .001$). In total, 24 of 53 patients (45%) were very satisfied with the PSAL treatment, and only 10 (19%) patients were very satisfied with the QSAL treatment ($P < .001$) (Table III).

Adverse events

A mean Visual Analog Scale pain score of 5.61 (SD 1.63) and 6.40 (SD 1.45) was reported for the PSAL and QSAL arms, respectively ($P < .001$). Transient, mild-to-moderate erythema and edema was experienced by all patients. The duration of postlaser scabbing was longer in the QSAL arm (8.07 ± SD 2.60 days) than the PSAL arm (7.79 ± SD 2.36 days; $P < .01$). Similar incidence rates of blistering were observed between the PSAL (10%, 27/279) and QSAL (11%, 33/311) arms ($P = .79$). Mild bleeding was reported in 1% (3/279) of the PSAL arm and 3% (8/311) of the QSAL arm ($P = .23$). Both blistering and bleeding resolved within a week after treatment.

PIH rates were lower after the PSAL treatment (26%, 14/53) than the QSAL treatment (34%, 18/53; $P < .001$). Similarly, the occurrence of PIHo was also less frequent in the PSAL arm (21%, 11/53) than the QSAL arm (47%, 25/53; $P < .001$). No patient healed with scar formation, textural changes, or other permanent events.

DISCUSSION

Although Q-switched lasers remain as the first-line treatment modality for nevus of Ota, accumulating data imply an equal or potentially better efficacy for PSAL. Chen et al reported a satisfactory result of PSAL on 4 patients with nevus of Ota; after an average of 3.5 treatment sessions, 1 patient

Fig 1. Lateral and front view of a 22-year-old female patient with nevus of Ota. before and after picosecond alexandrite laser and Q-switched laser treatments. **A1-A2**, Baseline appearance. *P* indicates picosecond alexandrite laser—treated area. *Q* indicates Q-switched laser—treated area. **B1-B2**, Twelve weeks after the first treatment session. **C1-C2**, Twelve weeks after the third treatment session. **D1-D2**, Final follow-up. *Tx*, Treatment.

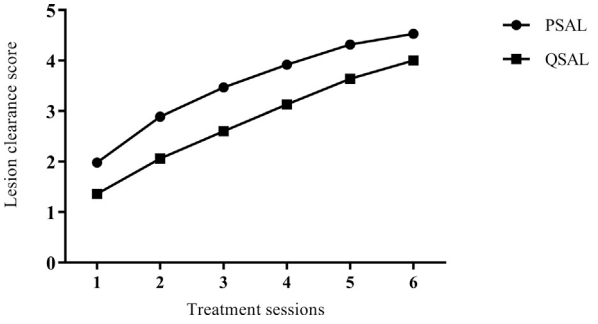

Fig 2. Nevus of Ota lesion clearance score by laser treatment session number. *PSAL*, Picosecond alexandrite laser; *QSAL*, Q-switched alexandrite laser.

Table III. Patients' satisfaction associated with laser treatments

	Patients, n/total (%)	
Likert satisfaction scale	**PSAL**	**QSAL**
5, very satisfied	24/53 (45)	10/53 (19)
4, satisfied	29/53 (55)	32/53 (60)
3, neither	0/53 (0)	11/53 (21)
2, dissatisfied	0/53 (0)	0/53 (0)
1, very dissatisfied	0/53 (0)	0/53 (0)

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

obtained a complete response (95%-100% lesion clearance), 2 an excellent response (75%-94% clearance), and 1 a good response (50%-74% clearance).[12] Peng et al also evaluated the effectiveness of PSAL for nevus of Ota.[18] After a single treatment, 8 of 29 patients achieved >75% clearance, 5 patients 50%-74% clearance. In Levin et al's study, a comparable efficacy was observed between PSAL and QSAL.[14] Chesnut et al further explored the use of PSAL on 3 nevus of Ota patients who were recalcitrant to multiple sessions of Q-switched laser treatments.[15] After 2-3 sessions, all lesions achieved significant lightening and cosmetic improvement. Though promising, these results were mostly derived from retrospective, uncontrolled case series.

In the present study, a prospective, evaluator-blinded, split-lesion controlled design was adopted to enable a direct comparison between PSAL and QSAL. PSAL, as was shown, was demonstrated to be a better treatment than QSAL for nevus of Ota. Fewer sessions of PSAL treatment led to greater lesion clearance. PSAL also outperformed QSAL with each treatment session, resulting in a faster onset of effect and a clear line of demarcation between the PSAL- and QSAL-treated parts within a lesion (Fig 1). The reason for this more favorable result after PSAL treatment is intriguing; our findings are similar to those reported for another dermal melanocytosis, acquired bilateral nevus of Ota-like macules, which responded more positively to PSAL treatment as well.[19] Both PSAL and QSAL generate ultrashort pulse durations (750 ps vs 70 ns), which are substantially shorter than the thermal relaxation time for the melanosome (0.25-1.00 μs) and melanocyte (100 μs).[23] When a desired therapeutic endpoint was reached, sufficient photothermal energy was supposed to be generated during laser irradiation. In fact, fluences used by PSAL were generally lower than QSAL in our study. Photomechanical effects under such circumstances might play a key role in addition to photothermolysis. According to Sun and Gerstman, as the laser pulse duration is shortened, tensile stress at the core of the melanosome grows without limit until an exploding threshold is reached, bringing about the fracture of melanosome and potentially the destruction of melanosome-containing cells.[24] The potent photomechanical effect intrinsic to PSAL might thus contribute to the better clearance which was observed.

Despite the use of topical anesthetics, laser treatment of nevus of Ota can still be painful. In our study, patients reported a moderate level of pain. PSAL treatment was perceived to be less painful than QSAL treatment, which agreed with a previous split-face study.[19] PIH and PIHo are common postlaser adverse events that occur in up to 20.9% and 11.9%, respectively, of the patients who received multiple sessions of QSAL treatment.[9] In our study, the PSAL arm showed fewer adverse events than the QSAL arm. In particular, the PIHo rate after PSAL treatment was considerably lower than that after the QSAL treatment (21% vs 47%), suggesting a protective role of lower photothermal energy on epidermal melanocytes. Meanwhile, it is notable that relatively high occurrences of PIH and PIHo were observed in this study. One possible reason for this was the 12-week treatment interval, during which some patients might not have fully recovered. In comparison, with an interval of 6 months to treat acquired bilateral nevus of Ota-like macules using PSAL and QSAL, Yu et al[19] reported low rates of pigmentary complications instead of the high rates that are usually reported.[25] Studies conducted with longer treatment intervals might therefore be needed to optimize the laser treatment of nevus of Ota among Asian patients.

One major limitation of this study was the lack of objective assessments. Photography-based assessments have their inherent limitations, even with the use of a stereotactic photography system. Also, the outcome measures used in this study were also subjective. Future studies with objective evaluations and outcome measures are warranted to validate our findings.

In conclusion, PSAL provided a more favorable clinical response with fewer treatment sessions, less pain, and fewer adverse effects compared with QSAL for the treatment of nevus of Ota.

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