

## Research Article

# Low-Fluence Q-Switched Nd: YAG Laser (LF-QSNY) May Be a Better Choice for the Treatment of Early Nevus of Ota: A Prospective Self-Controlled Trial of LFQS and Picosecond Alexandrite Laser

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Received 28 November 2023; Revised 23 January 2024; Accepted 24 January 2024; Published 19 March 2024

Academic Editor: Marc Zachary Handler

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**Background.** Low-fluence Q-switched Nd: YAG laser (LF-QSNY) and picosecond 755 nm alexandrite laser (PSAL) have shown superiority in the treatment of nevus of Ota (NO). **Objective.** To compare the efficacy and safety of PSAL and LF-QSNY in the treatment of NO. **Methods.** 15 patients randomly underwent split-lesion treatment of the two lasers within three months. The visual analogue scale (VAS) was used to evaluate the efficacy outcomes. The patient's preferences, recurrence rate, and adverse events were also documented. **Results.** Fifteen patients with 34 lesions finished the trial. Lesions, operated with LF-QSNY and PSAL, reached VAS scores of  $3.47 \pm 0.67$  and  $3.51 \pm 0.87$ , respectively ( $P > 0.05$ ). Most significant improvement in LF-QSNY was achieved after the first session (VAS = 1.84). One (6.67%) patient experienced a relapse on the PSAL side. Temporary hypopigmentation and hyperpigmentation mainly occurred on the PSAL side. Patients under five years demonstrated superior efficacy ( $3.81 \pm 0.47$  vs  $3.08 \pm 0.66$ ,  $P = 0.046$ ) than those over with the treatment of LF-QSNY. **Limitations.** Limited sample and lack of objective evaluation. **Conclusion.** The difference between the LF-QSNY and PSAL in the treatment of NO was statistically insignificant, while LF-QSNY may be a better choice for the treatment of early NO. This trial is registered with ChiCTR1900022690.

## 1. Introduction

Nevus of Ota, a benign melanocytic nevus, mainly presents as speckled or mottled, brown to blue-green patches on the face, more specifically, on where it is innervated by the branches of the trigeminal nerve [1]. Nevus of Ota is most commonly found in Asian ethnicity and usually involves unilateral face. Pathologically, dendritic melanocytes appear in the dermis [2, 3]. Though with a benign course, nevus of

Ota brings cosmetic problems and many research studies have focused on the treatment.

Abundant research studies have proved the efficacy of the Q-switched Nd: YAG laser (QSNY) and Q-switched alexandrite laser (QSAL) on nevus of Ota [4]. Recently, novel low-fluence QSNY has also been proved effective in the treatment of nevus of Ota with similar effect and minimal complication rates [5, 6]. This technique seems to be a promising method for patients, especially at young ages.

On the other side, the picosecond alexandrite laser (PSAL) has also proved higher clinical efficacy and lower adverse effects, especially compared with those of traditional QSL [7].

However, a comparison between PSAL and LF-QSNY for nevus of Ota is lacking. Therefore, this study aims to compare the efficacy and safety of the two lasers for the treatment of nevus of Ota.

## 2. Materials and Methods

**2.1. Study Design.** This study was conducted in the Department of Laser and Aesthetic Medicine, Shanghai Ninth People's Hospital, from June 2019 to July 2021. Patients were included if they were healthy subjects with untreated Nevus of Ota. Meanwhile, exclusion criteria were as follows: combined with other related diseases, during pregnancy or planning to be pregnant, wound or any skin complaint at treated site, allergic to local anesthetics, and participation in other clinical trials. Patients and/or their parents fully understood this clinical trial (Chinese Clinical Trial Registration Number: ChiCTR1900022690) and have signed the informed consent. This study has been approved by the institutional ethics committee of Shanghai Ninth People's Hospital (SH9H-2019-T48-1) (Figure 1).

**2.2. Laser Treatment.** Each patient's nevus of Ota lesion was allocated to be treated with PSAL and LF-QSNY. The sites for two treatments were selected by randomized sequences (<https://www.random.org>). The patients who were assigned an odd number were treated by PSAL on the left or top test site and LF-QSNY on the right or bottom test site. Patients who were assigned an even number received contrary treatment [8]. Topical anesthetic (EMLA cream: 2.5% lidocaine and 2.5% prilocaine) was applied 1 hour prior to laser treatments. Ice bag was applied for 15 min to reduce tissue edema and pain after the operation.

Treatment parameters are as follows:

- (1) PSAL group: 5.25–6.37 J/cm<sup>2</sup> energy, 5 Hz frequency, 2 mm spot, and one pass without overlap (Picosure; Cynosure, Westford, MA). The clinical end point is immediate whitening.
- (2) LF-QSNY group: 1.8–2.2 J/cm<sup>2</sup> energy, 10 Hz frequency, 8 mm spot, and 8 to 12 passes (Spectrum; Lutronic). The clinical end point is mild to moderate erythema with few petechiae.

Treatment has a two-stage process. First, each subject was treated with PSAL for one time and LF-QSNY for six times in a three-month comparative trial. Then, each patient selected a preferred laser for after-treatment of the lesions. The interval for PSAL and LF-QSNY is 3 months and 2 weeks.

**2.3. Evaluation.** Patients' demographic data were collected, including sex, age, sclera pigmentation, lesion color, and Tanino classification. Patients took standardized photographs every two weeks during the first phase and each visit

during the second phase with the same camera (60D camera; Canon, Melville, NY). Three blinded physicians independently evaluated the improvement using the visual analog scale (VAS) every two weeks: score 5, complete improvement, clearance of 95%–100%; score 4, excellent improvement, clearance of 76%–94%; score 3, good improvement, clearance of 51%–75%; score 2, fair improvement, clearance of 26%–50%; score 1, poor improvement, clearance of 0%–25%. Mean score was adopted. At the final follow-up visits, patients' satisfaction was recorded using the Likert scale (very dissatisfied, score 1; dissatisfied, score 2; neither, score 3; satisfied, score 4; and very satisfied, score 5).

In addition, reasons for choosing either laser for subsequent treatment, adverse reactions (postinflammatory hypopigmentation (PIHo), postinflammatory hyperpigmentation (PIH), uneven pigmentation, and scars), and recurrence were recorded during visits.

**2.4. Data Analysis.** GraphPad Prism 8 and SPSS 21.0 statistical software were used for statistical analysis. The efficacy of two lasers was compared by the Wilcoxon test, and McNemar's test was used to compare the adverse event and recurrence rate. The consistency of assessment among different observers was analyzed by the intraclass correlation coefficient (ICC) and was defined as follows: poor, ICC ≤ 0.50; moderate, 0.50 < ICC ≤ 0.75; good, 0.75 < ICC ≤ 0.9; excellent, ICC > 0.9. In addition, Fisher's exact test was used to analyze the correlation between effect and age, gender, lesion color, sclera pigmentation, and Tanino classification [9, 10]. Difference was defined as statistically significant when  $P < 0.05$ .

## 3. Results

**3.1. Patient Information.** Seventeen patients were enrolled, and 15 patients (three male and 12 female) with 34 lesions have finished the trial (Table 1). The mean age of treatment initiation was 8.02 ± 9.38 (0.4–29) years. Detailed clinical characteristics are shown in Table 1.

### 3.2. Treatment Results

**3.2.1. Visual Assessment.** All patients (15 cases with 34 lesions, two patients with two discontinued lesions) were treated with LF-QSNY six times and one PSAL treatment within three months (Figures 2 and 3). The consistency of the evaluation results was good as the ICC reached 0.808 ( $P < 0.001$ ). After the three-month treatment, the average VAS scores were 3.51 ± 0.87 and 3.47 ± 0.67 on the side treated by PSAL and LF-QSNY, respectively ( $P > 0.05$ ).

In addition, as treatment mounted up, the efficacy of LF-QSNY gradually increased (VAS increased from 1.84 to 3.47) every two weeks. Most significant improvement in LF-QSNY was achieved after the first session (VAS = 1.84). Meanwhile, VAS scores on the side which was received one PSAL treatment also steadily increased (2.69 to 3.51) within 12 weeks (Figure 4).

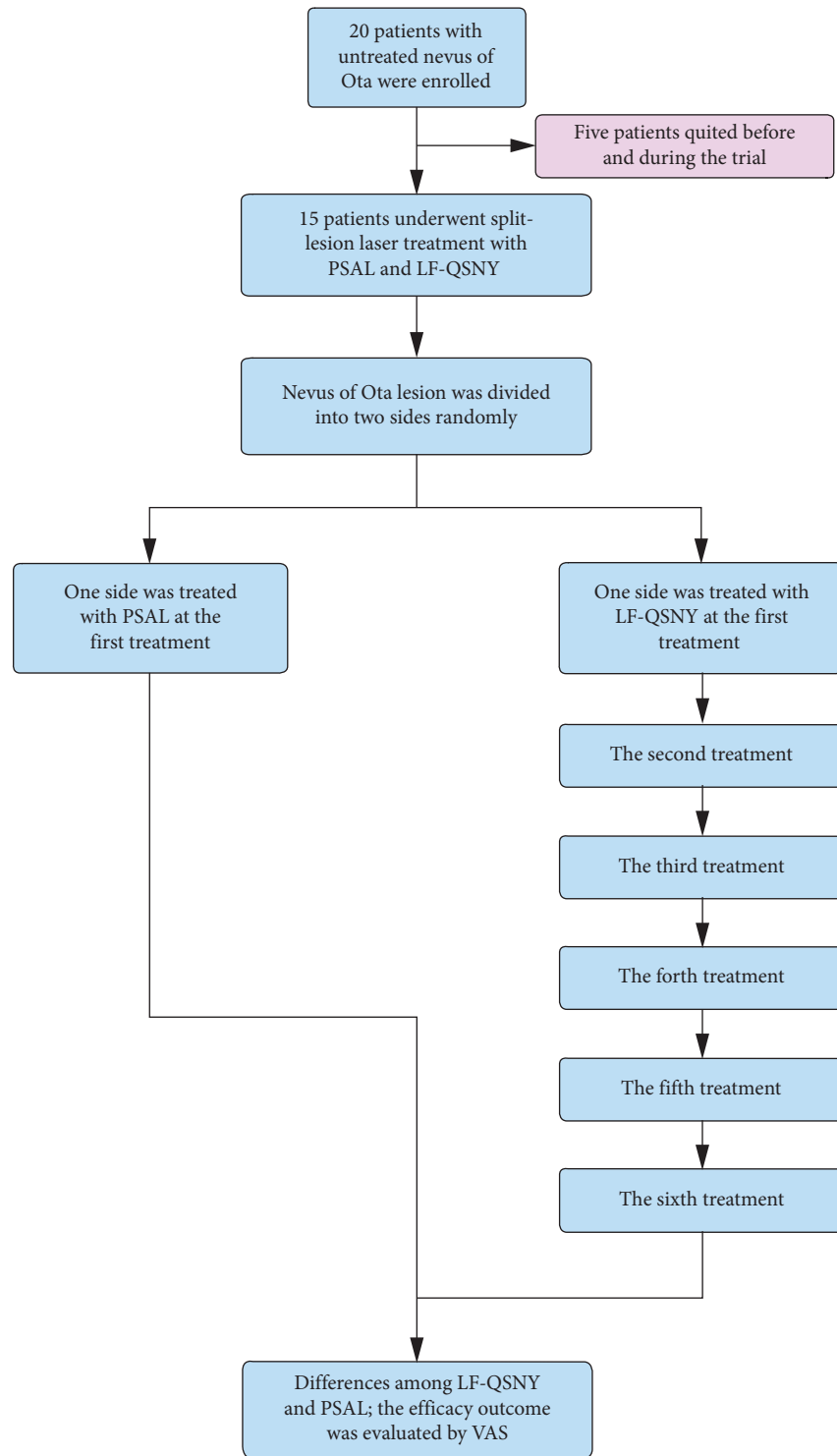


FIGURE 1: Participant enrollment, randomization, and analysis.

After the comparative treatment, 46.67% ( $n = 7$ ) of patients chose LF-QSNY therapy and 53.33% ( $n = 8$ ) of patients chose PSAL therapy. The final VAS was  $4.33 \pm 0.47$  and  $4.54 \pm 0.31$  in the PSAL with an average treatment session of 3.33 times (range 2–5) and LF-QSNY with an average treatment session of 15.62 times (range 8–24), respectively ( $P > 0.05$ ). Patients who chose LF-QSNY were significantly

younger than patients who chose PSAL ( $2.60 \pm 0.841$  vs  $12.76 \pm 3.83$ ,  $P = 0.002$ ). The follow-up time ranged from 10 to 24 months (average 18.51 months).

**3.3. Analysis of Influencing Factors.** Patients younger than five years demonstrated superior efficacy ( $3.81 \pm 0.47$  vs  $3.08 \pm 0.66$ ,  $P = 0.046$ ) than those older than five years with

TABLE 1: Demographic information.

Demographic information (N=15)	Measurement n (%)
Age (years)	Average 8.02 ± 9.39, range (0.4–29)
Sex	
Female	12 (80%)
Male	3 (20%)
Tanino classification	
I	3 (20%)
II	3 (20%)
III	7 (46.67%)
IV	2 (13.33%)
Color of lesions	
Blue-violet	7 (46.67%)
Brown	5 (33.33%)
Brown-violet	3 (20%)
Sclera pigmentation	
Yes	5 (33.33%)
No	10 (66.67%)

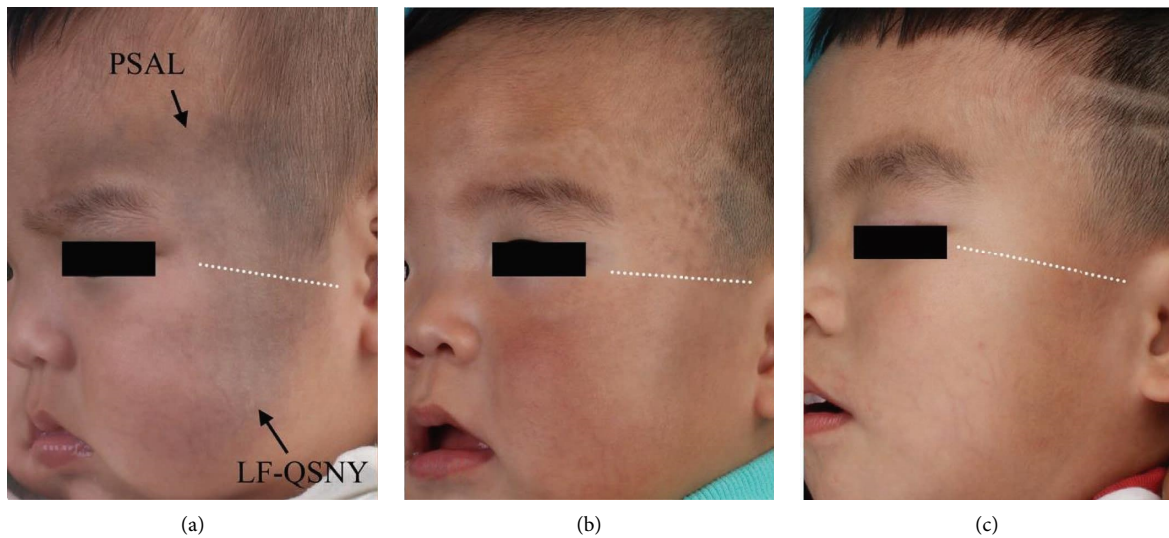


FIGURE 2: Male patient, 4.8 months old. (a) Before treatment; (b) two weeks after sixth treatments with LF-QSNY on the lower part; 12 weeks after one treatment with PSAL on the upper part; (c) after the comparative trial, the patient's guardian chose LF-QSNY for follow-up treatment. Two weeks after another 18 sessions of LF-QSNY treatments, the lesions were completely removed.

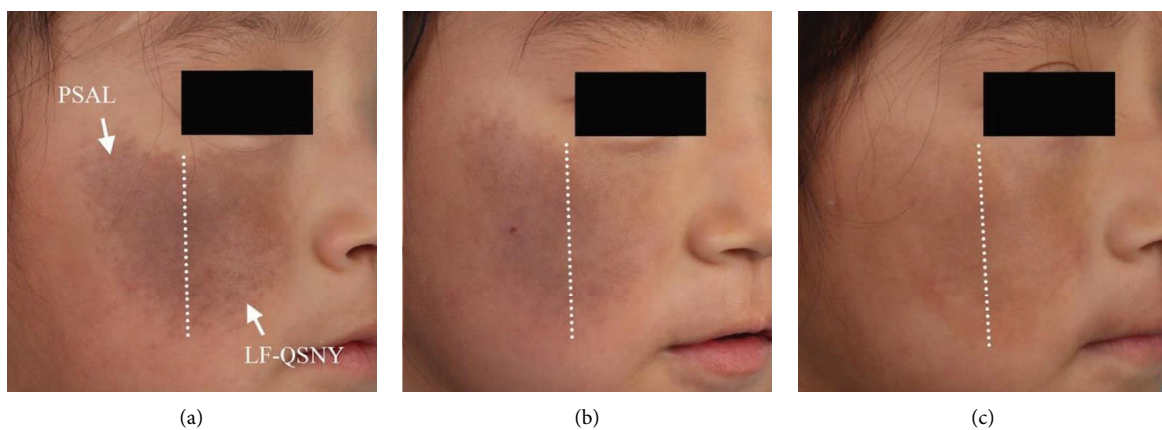


FIGURE 3: Female patient, 6 years old. (a) Before treatment; (b) three months after one treatment with PSAL on the left; two weeks after sixth treatment with LF-QSNY on the right; (c) eight months after additional five sessions of PSAL, part of the lesion has been cleaned.

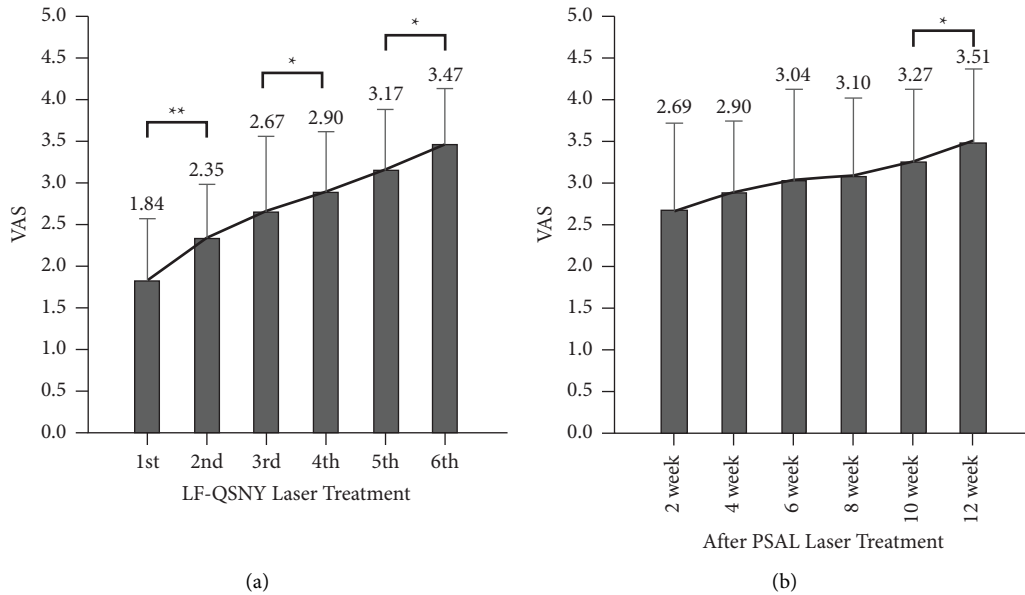


FIGURE 4: (a) Visual evaluation after each LF-QSNY VAS scores. The VAS score differences before and after each laser treatment were 0.51, 0.32, 0.23, 0.27, and 0.30, respectively. The difference between each two sessions was significant ( $P < 0.01$  and  $P < 0.05$ ). (b) Visual evaluation within 12 weeks after one treatment of PSAL. The VAS score differences were 0.21, 0.14, 0.06, 0.17, and 0.24, respectively. The VAS score was steadily increased but was only significant at the final visit ( $P < 0.05$ ). \* means  $P < 0.05$  and \*\* means  $P < 0.01$ .

the treatment of LF-QSNY. With the treatment of PSAL, however, no significant correlation was found between age and clearance ( $P > 0.05$ ). The efficacy of the laser treatment had no relation with patient's Tanino classification, gender, sclera pigmentation, and lesion color (Figure 5).

**3.4. Safety Assessment.** During the first three months, eight patients (53.33%) experienced PIHo on the side treated with PSAL (Figure 6). The remission time for six of these patients ranged from 2 to 10 weeks, and one patient who had selected PSAL experienced PIHo for a half year, and the other one who had selected LF-QSNY still had PIHo 21 months after treatment. Meanwhile, three (20%) patients developed temporary PIH on the PSAL side and recovered in two to eight weeks.

On the LF-QSNY-treated side, one patient (6.67%) developed slight PIH and recovered in four weeks. No hypopigmentation had been observed.

No patient experienced relapse on the LF-QSNY-treated side, while one patient experienced a slight relapse on the PSAL-treated side with brown spots reappearing on the lesions at 12-month follow-up.

No patients showed scars.

Patients who chose LF-QSNY were more satisfied, as all patients scored 5 (very satisfied), while only two patients who chose PSAL rated 5-score and six rated 4-score (satisfied) ( $P < 0.001$ ).

#### 4. Discussion

Targeting melanosome-laden melanocytes, Q-switched lasers have advanced the management of nevus of Ota [11], and various wavelengths, mainly, alexandrite (755 nm) and

Nd: YAG (1064 nm), were used extensively [12–17]. In order to obtain a higher clearance, relatively high fluence usually would be adopted [18]. However, these practices may inevitably induce side effects, including PIH, PIHo, and scars, especially in Asian patients with darker skin [13, 19–21]. In report, the highest PIH rates were 20.9% for QSAL and 10.6% for QSNY; PIHo rates were 11.9% for QSAL and 22.9% for QSNY; scarring rates were 3.2% for QSAL and 4.4% for QSNY [14, 19–21]. Thus, it is important to further reduce the side effects, especially in young children.

The Q-switched Nd: YAG (1064 nm) laser utilizes the concept of selective photothermolysis to target the melanin in Ota's nevus, and the wave length of 1064 nm can reach deeper targets as the abnormal melanocytes existed in the dermal layer. It is estimated that this wave length is the preferred choice for dark-skinned patients because of minimization of epidermal injury. Low-fluence QSNY with multipass and more sessions brings subcellular selective photothermolysis with minimal inflammation [22]. On the other hand, the ultrashort pulse equipped by a picosecond laser and additional photoacoustic effect makes it possible to reduce photothermal effects to the surrounding tissue and minimizing thermal damage [23]. Though both techniques have been successfully applied to nevus of Ota [5, 6, 24], recent studies only presented as retrospective, uncontrolled series. Therefore, our study firstly compared the efficacy of LF-QSNY and PSAL by prospective, evaluator-blinded, split-lesion-controlled design.

As shown, the overall effectiveness between LF-QSNY and PSAL within three months was not significantly different in the treatment of nevus of Ota. Further careful evaluation showed that five patients (33.33%) responded significantly different to these two types of laser treatments (VAS difference  $\geq 1$  between the two laser treatments'

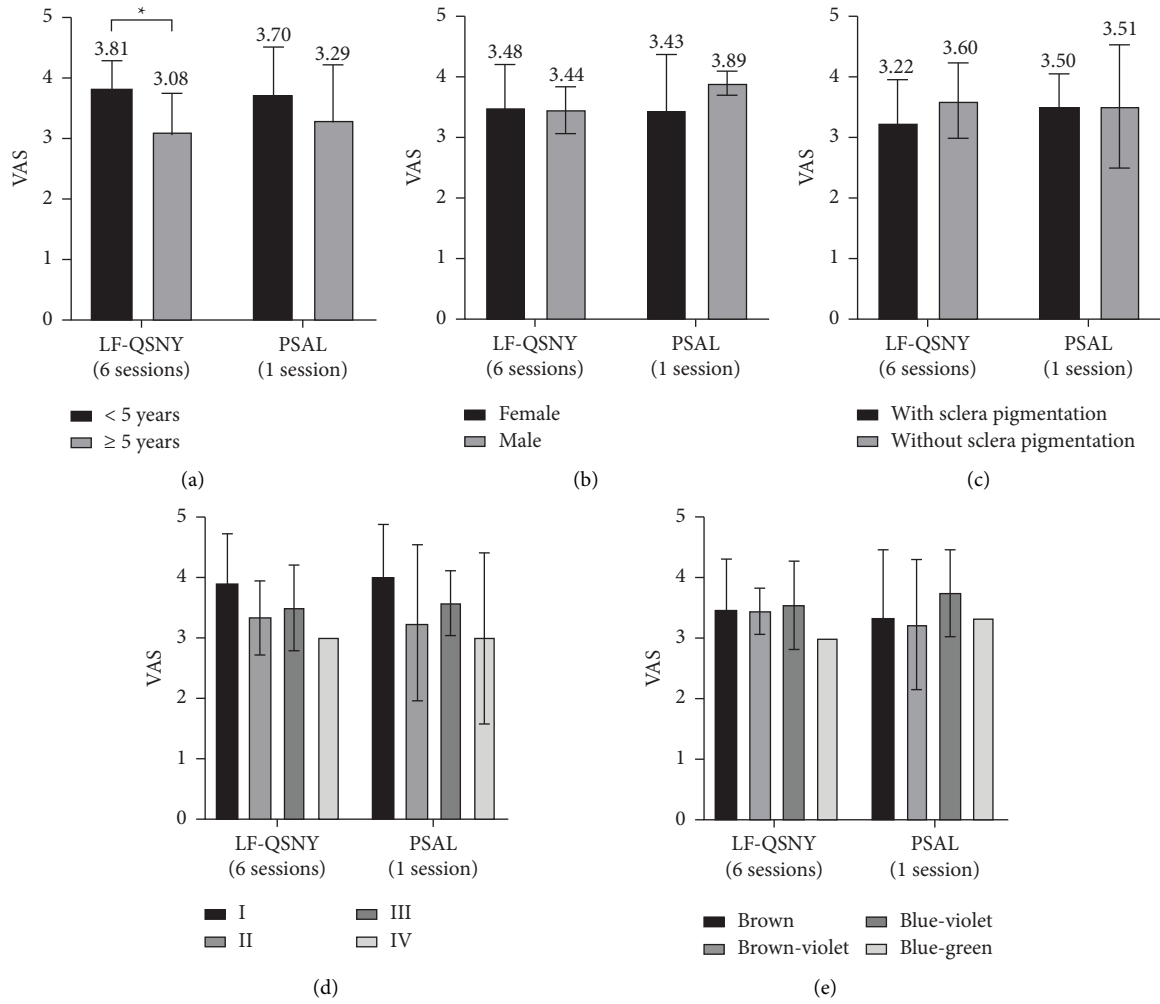


FIGURE 5: Analysis of influencing factors. (a–e) Laser efficacy of patients with different ages (less than or equal to 5 years old versus greater than 5 years old), genders (male versus female), sclera pigmentation, Tanino classification, and lesion color. \* means  $P < 0.05$  and \*\*  $P < 0.01$ .

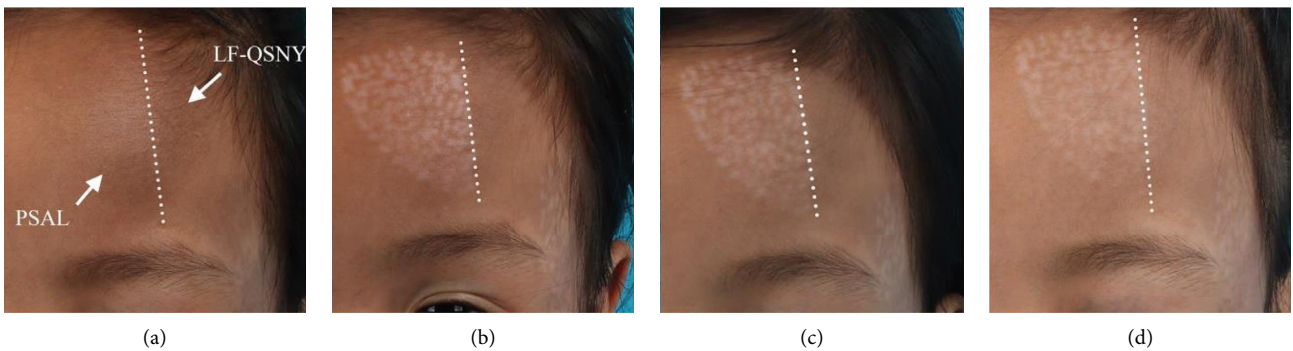


FIGURE 6: Continued.

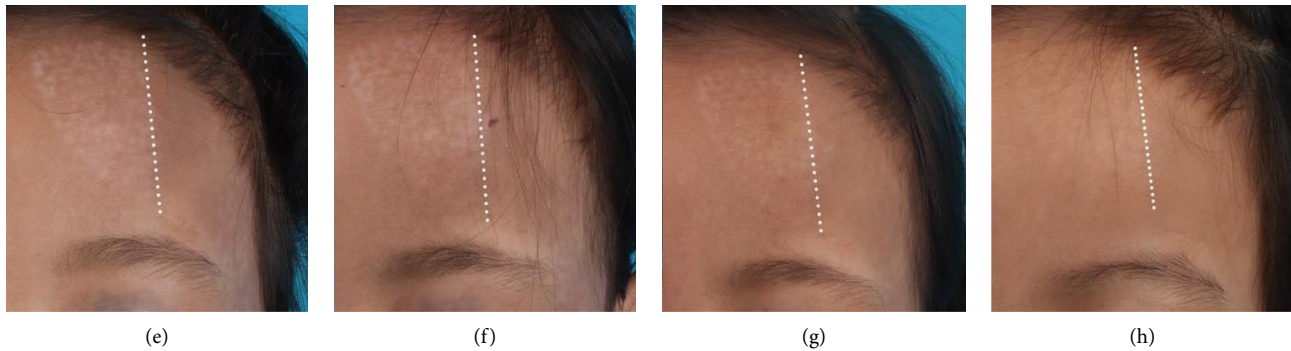


FIGURE 6: Female patient, 6 years old. (a) Before treatment; (b–g) 2, 4, 6, 8, 10, and 12 weeks after one treatment with PSAL on the left and two weeks after first, second, third, fourth, fifth, and sixth treatments with LF-QSNY on the right; (h) two weeks after 12 additional treatments with LF-QSNY, the lesion has been completely removed. Slight hypopigmentation can be still observed on the PSAL treated side.

efficacy); among them, PSAL was superior in three patients, while LF-QSNY was superior in two patients. The possible reason for the better efficacy of the picosecond laser may be that PSAL fluence was high enough to generate sufficient photothermolysis to damage those dermal melanocytes in nevus of Ota, thus leading to more lesion clearance. On the other hand, the possible reasons for the better efficacy of LF-QSNY may be that the photothermal damage for the picosecond laser was relatively high that PIH had been raised and not fully recovered by three months, or the damaged melanocytes had not achieved full degradation at three-month follow-up since further improvement had been noted by some clinicians at six months to one year after the last treatment [7, 25]. The results suggest that an initial test patch is necessary for subsequent treatment of nevus of Ota.

It was found that the effect of LF-QSNY gradually increased after each treatment; the most conspicuous improvement was observed after the first session. Therefore, LF-QSNY steadily cleaned the lesion of nevus of Ota after each treatment, but the removal of the lesions would be more noticeable after the first treatment, which was different to our previous study on its efficacy for café-au-lait macules (CALMs). The different depths and features of pathological melanocytes in nevus of Ota and CALMs might be the reason of the difference of eliminating process. The LFQS laser had obvious lesion clearance after the first treatment. While both research studies indicated with the increase of LF-QSNY treatment sessions, the clearance of lesions gradually accumulated [26].

On the PSAL-treated side, lesions also steadily improved after treatment. The VAS score improved from 2.69 to 3.51 for the PSAL-treated side between two weeks after treatment and three months after treatment. The results indicated that the pigment particles would be gradually removed by the macrophages, which manifested very differently from that of epidermal pigment disease. The latter efficacy was stable from the time the scab was removed, which was about from two weeks to 12 weeks posttreatment [8].

For the PSAL-treated side, temporary depigmentation occurred on 53.33% of patients ( $n=8$ ), and the average resolving time for most cases was 2 to 12 weeks; however, one patient experienced PIHo for a half year; the other experienced for more than 21 months; and 20% of patients

experienced temporary hyperpigmentation, which resolved in two to eight weeks. For the LF-QSNY-treated side, only one patient experienced slight PIH, which resolved within four weeks. The higher PIHo rates reported by our study on the PSAL side may be due to the shorter follow-up time than that used in former studies, and the fluence used in our study is higher. In addition, we found more evenly pigmentation on the LF-QSNY-treated side during the early treatment, which resulted in more acceptable appearance improvement, though eventually, two lasers brought equal clearance on the lesion pigmentation.

PSAL therapy is preferred by older children and adults (50% among the further choices for PSAL) in order to get a better outcome ( $n=4$ ) or to balance their busy school or work lives ( $n=4$ ), while low-fluence technology was more popular among young patients for the following specific benefits. First, the complication rates, including erythema, swelling, and scabbing on the LF-QSNY, would be significantly lower, which would reduce the caring time for the guardians. Faster pain and burning resolution will also reduce a child's symptoms of crying, restlessness, and fear, as reported by guardians. Also, adopting LF-QSNY leads to faster recovery. The mean treatment sessions for the LF-QSNY were 15.62 (8–24), which means patients can finish the session within four months. While the mean treatment sessions for PSAL were two to five, usually three-to-six-month intervals between sessions were recommended, which would take the mean at least 6 months for PSAL treatments and may even be longer than 30 months [27]. Further treatments and shorter periods for overall recovery are ideal to limit psychosocial impacts in young patients [6].

During the follow-up, we found only one (6.67%) relapsed patient, which manifested as slight brown spots on the cured lesion at one-year follow-up after treatment. This patient chose the LF-QSNY laser, and the lesion was completely cleared; however, the relapse was on the PSAL side. Reported recurrence rate after high-fluence laser treatment was 0.6–1.2% [10], but higher recurrence was reported in younger patients with a rate of 15.4% [28]. The possible explanation for this relapse happened only on the PSAL side may be that the melanin-deficient melanocytes after the PSAL laser gradually accumulated melanin which would exaggerate pigment and

trigger recurrence after complete clearance, while frequent and multiple LF-QSNY laser irradiation cumulates photo-toxic damage on melanocytes, which causes a decrease in melanogenesis and atrophy of melanocyte dendrites [29, 30].

In conclusion, based on patient's choice, LF-QSNY would be more preferred than PSAL among young patients due to the significantly reduced side effects and downtime. Also, LF-QSNY achieves good efficacy in younger children (less than five years old) and requires a short recovery time; thus, patients can conduct more sessions of laser in the same period, and younger children can achieve complete lesion removal quicker with slighter wound healing processes.

The limitations of our research were the lack of sample size and objective evaluation. Prospective clinical trials with objective evaluation and larger sample sizes are necessary to further confirm our conclusion and results.

## 5. Conclusion

The difference between the LF-QSNY and the PSAL in the treatment of nevus of Ota within a three-month comparative trial was statistically insignificant. However, LF-QSNY is more welcomed by young patients and their guardians; it is likely to bring the best outcome in a shorter period and cause less temporary adverse reactions in the meantime than PSAL. While PSAL may be a better choice for those preferring fewer visits and treatments, obvious lesion clearance might be observed after the first treatment of LF-QSNY, and an initial test patch is suggested.

## Data Availability

The data used to support the findings of this study are available from the corresponding author on reasonable request.

## Conflicts of Interest

The authors declare that there are no conflicts of interest.

## Authors' Contributions

Lucia Zhou, Jiafang Zhu, Qingqing Cen, Xiaojie Hu, Gang Ma, and Xiaoxi Lin contributed equally to this work and Lucia Zhou, Jiafang Zhu, and Qingqing Cen are listed as co-first authors.

## Acknowledgments

This study was funded by the Project of Biobank (YBKA201902) and Clinical Research Program (JYLJ001) from Shanghai Ninth People's Hospital and grants of the National Natural Science Foundation of China (No. 81602777) and project ZR2021QH291 supported by the Shandong Provincial Natural Science Foundation.

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