Q-PTP is an optimized technology of 1064-nm Q-switched neodymium-doped yttrium aluminum garnet laser in the laser therapy of melasma: A prospective split-face study

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Abstract. Quickly-pulse-to-pulse (Q-PTP) is the latest dual pulse mode Q-switched neodymium-doped yttrium aluminum garnet [QS Nd:YAG (QSNY)] laser technology that improves efficacy and minimizes side effects. In this study, the safety, efficacy, and advantages of Q-PTP and single-pulse laser mode of 1064-nm QSNY in the treatment of melasma were compared. Twelve healthy women were enrolled in this split-face study. Q-PTP and single-pulse laser mode of 1064-nm QSNY were applied to the treatment side and the control side, respectively. Physician's global assessment, patients' self-assessment and the modified melasma area and severity index (mMASI) scores were used to quantify pigmentation changes. Side effects were recorded. Mean mMASI scores were decreased significantly at the 4th and 12th-week follow-up visit compared to the baseline. Melasma lesion clearance was more than 50% in 58% of patients compared with the baseline. However, both sides of the same patient showed similar therapeutic effect. Minor pain experience and slighter skin erythema reaction were reported in Q-PTP laser mode treatment side compared with the control. No serious complications were found in any of the patients. Q-PTP laser mode of 1064-nm QSNY is an optimal laser therapy in the treatment of melasma with greater safety and superiority.

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Introduction

Melasma is an acquired disorder of hyperpigmentation that typically presents as symmetric hyperpigmented macules on the sun-exposed areas of skin, especially on the face (1). Although no race is spared, melasma is particularly common in women at the reproductive age whose skin types are Fitzpatrick III-V. Chronic sunlight exposure, genetic factors, pregnancy, and sex hormones are generally believed to be related to the occurrence of melasma (2). Moreover, improper use of cosmetic and over-scrubbing of the face have been proposed (3), but the pathogenesis and etiology of melasma have not yet been fully elucidated.

The treatment of melasma is challenging and difficult since it is refractory and patients often suffer relapse. Currently, the 1064-nm, low-fluence Q-switched neodymium-doped yttrium aluminum garnet [QS Nd:YAG (QSNY)] laser is a commonly used laser treatment of melasma. The 'laser toning' technique was used for melasma treatment, and most of the studies have been conducted in Asians (4-6). The technique includes large spot sizes, low fluences, and multiple passes, and it is performed in five to ten sessions at weekly to monthly interval. Subcellular-selective photo-thermolysis was described as the mechanism that selectively destroyed melanin while melanocytes were kept intact (7,8). Mild treatment, lower incidence of complications and minimal downtime are the advantages of this laser therapy.

Quickly-pulse-to-pulse (Q-PTP) is the latest dual pulse mode QS Nd:YAG laser technology that improves efficacy and minimizes side effects by creating higher peak energy and more effective photo-mechanical destruction of melanin particles (Fig. 1). There are some previous reports regarding the efficacy and safety of low-fluence Nd:YAG laser therapy for melasma, but few studies have explored the laser toning with Q-PTP laser mode (9,10).

We performed a prospective split-face study to compare the degree of improvement and side effects of different modes of laser toning with 1064-nm QS Nd:YAG laser in the treatment of melasma. The aim of this study was to explore the advantages, efficacy, and safety of laser toning with Q-PTP mode in treating melasma in Chinese patients.

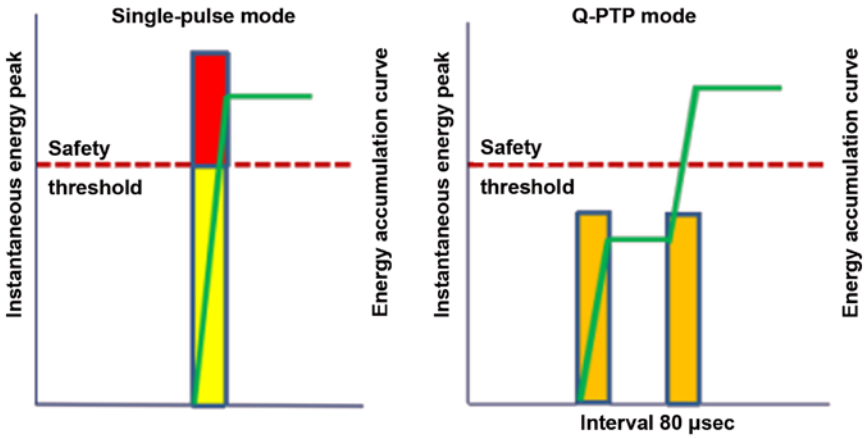

Figure 1. Q-PTP, in which one pulse is split into successive two sub-pulses by 80 μsec intervals and two relatively weak energy pulses are accumulated to produce higher peak power than those produced by the current QS single-pulse. Q-PTP, quickly-pulse-to-pulse.

Patients and methods

Patients. From March 2016 to March 2017, twelve healthy women ageed from 29 to 45 years with mild to severe symmetrical melasma with skin types III or IV were consecutively enrolled. Subjects were recruited from the Outpatient Department of Dermatology and Aesthetic Surgery in Zhongshan Second People's Hospital (Zhongshan, China). The exclusion criteria ruled out women with pregnancy or breast feeding, any hormonal therapy, laser or intense pulsed light therapy in the past 3 months, using topical bleaching agents in the past 3 months, other medication treatments in the past 3 months, inflammatory disease of the facial skin, history of photosensitivity-related disorders, and over-expectation of the treatment. QS 1064-nm Q-PTP laser mode was used to treat the right side of the faces of the patients, while the single-pulse was used on the left sides and the pre-treatment as control.

We explained the procedures, benefits, risks and potential complications of the procedure to all the subjects. Written informed consent was obtained from all patients or guardians before the enrollment in accordance with the Declaration of Helsinki. This clinical study was approved by the Ethics Committee of Zhongshan Second People's Hospital. The patients provided consent for the data to be published.

Laser treatment. This was a random study. The skin was cleansed using a mild cleanser before treatment. Standard digital photographs (Canon EOS 600D) were taken from the front and side of both cheeks before and after each treatment session.

All subjects were assigned to the split-face study, and treated with 1064-nm QS Nd:YAG laser (Spectra VRMIII®, Lutronic Corp.), collimated homogeneous flat-top beam profile, 5-7 nsec pulse width and 7 mm spot size. Q-PTP and single-pulse laser mode were applied to the treatment side and the control side, respectively. The fluence was 1.8 J/cm^2 (0.9 J/cm^2 each sub-pulse in Q-PTP mode), and the treatments were repeated with 1,600 spots each side with appropriate overlap (approximately 10%), regardless of the development of erythema and swelling. The treatment was administered for a total of five sessions at 4-week intervals. A cooling collagen containing mask was applied after each session. To ensure consistency, all laser treatments were performed by the same therapist. Patients were followed up at the 4th and 12th week after the final laser treatment.

Broad-spectrum Sunscreen with a sun protection factor (SPF) 30+ and protection Ultraviolet A (PA)+++ was instructed to be used on the whole face to avoid direct sun exposure during the entire study period.

Immediate post-treatment assessment. The patients and assessors were double-blinded. The degree of erythema and the procedural pain were evaluated immediately after the first treatment session in each side treated with QS 1064-nm Q-PTP and single-pulse modes, by two assessors (one dermatologist and one plastic surgeon), independently. Patients were asked to rate treatment pain and chose a number that represents their pain on both sides of the face based on a numerical rating scale range 0-10 (0, no pain; 10, worst pain). Pain scores were divided into four grades: 0, none (0); 1, mild (1-3); 2, moderate (4-6); and 3, severe (7-10). Skin erythema reaction assessment was performed using a clinical assessment scale of 0, none; 1, mild; 2, moderate; and 3, severe (swelling, petechiae, and other serious skin reactions).

Clinical efficacy. Two assessors (one dermatologist and one plastic surgeon) evaluated each half of the face used a modified melasma area and severity index (mMASI) score based on the patients' photos at baseline and after the final laser treatment at the 4th and 12th week follow-up. The mMASI was used to score patients melasma based on the percentage of the total area (A), darkness (D), and homogeneity (H) of pigment lesions involving the forehead, cheek, and chin on each side of the face. The sum of the severity grade used three factors and the calculations as shown in Table I.

Physician's global assessment. Two blinded assessors (one dermatologist and one plastic surgeon) assessed the results of treatment based on the patients' photos. A six-grade VAS (visual analog scale) assessment was designed to compare four weeks' follow-up records with the baseline, and melasma clearance on both sides of the face. Improvement of melasma as follows: excellent (melasma clearance >75%); good (melasma clearance 50-75%); moderate (melasma clearance 25-50%); minimal (melasma clearance <25%); unchanged (no clearance); worsening (complications occurred).

Table I. Modified melasma area and severity index (mMASI) score.

	0	1	2	3	4	5	6
Area (A)	0%	1-9%	10-29%	30-49%	50-69%	70-89%	90-100%
Darkness (D)	Absent	Slight	Mild	Marked	Severe		
Homogeneity (H)	Absent	Slight	Mild	Marked	Severe		

MASI = Area x (Darkness of pigment + Homogeneity)

Modified MASI score = (f) 0.15A(D+H) + (m) 0.3A(D+H) + (c) 0.05A(D+H)[a]

[a]Modified melasma area and severity index (mMASI) score counted on each half of the face. f, forehead; m, malar; c, chin.

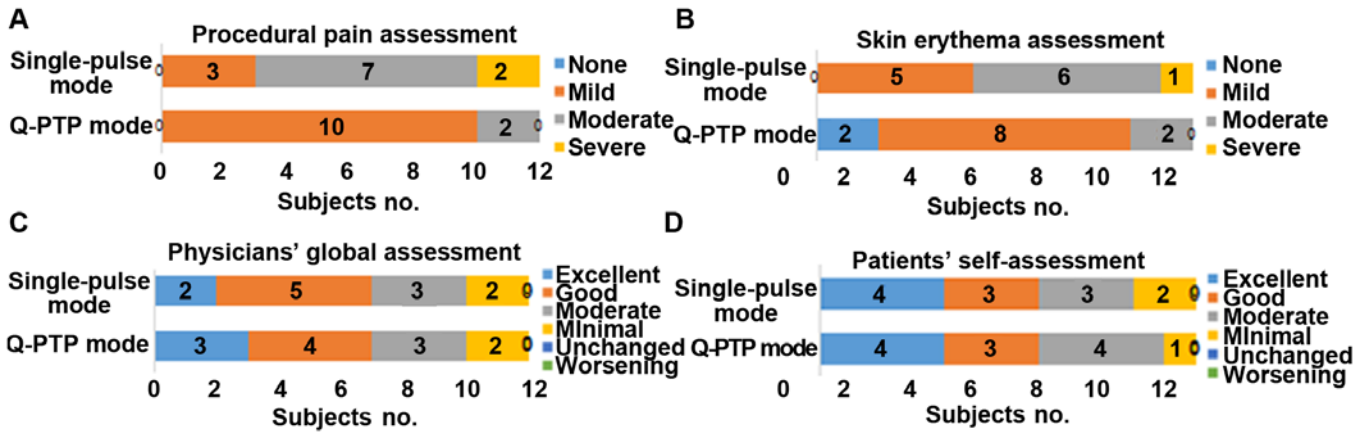

Figure 2. (A) Minor pain experience and better patient acceptance were reported in Q-PTP laser mode treatment side (P<0.05). (B) Slighter skin erythema reaction was reported in Q-PTP laser mode treatment than the control treatment (P<0.05). (C and D) Melasma improvement showed a positive treatment efficacy at the 4th week follow-up. However, the same patient on both sides of the face showed similar therapeutic effect (P>0.05). Q-PTP, quickly-pulse-to-pulse.

Patients' self-assessment. Patients' subjective satisfaction with the results rated through photos, using the same six-grade VAS assessment.

Safety assessment and recurrence. At each treatment and follow-up, adverse events (AE) of patients were recorded. If adverse effects were detected, they were treated promptly. At the same time, other side effects and complications were recorded during and after the study including swelling, petechiae, burning, itching, facial dryness, hyperpigmentation and hypopigmentation or punctate leucoderma.

Patients were asked to use sun protection and avoid sunlight exposure to reduce the effect of the sunlight on treatment. At the 4th and 12th-week follow-up visits after the final laser treatment, increase of the lesions or worsening of hyperpigmentation was considered as a recurrence.

Statistical analysis. Data statistical analysis was conducted with Statistical Package for Social Sciences (SPSS) software version 19.0 (IBM Corporation). mMASI scores were reported as the means ± standard deviation. A paired t-test was used to compare mMASI reductions. Differences in grades of procedural pain, skin erythema reaction, physician and patients' self-assessments of both sides of the face were tested using the Wilcoxon signed-rank test, before and after the therapy. Two-tailed P<0.05 was considered to indicate a statistically significant difference.

Results

Procedural pain and skin erythema assessment. Treatment pain scores in QS 1064-nm Q-PTP and single-pulse laser mode applied to the treatment side and the control side, respectively, were none (0 vs. 0), mild (10 vs. 3), moderate (2 vs. 7) and severe (0 vs. 2) (Fig. 2A). There was a statistically significant difference (P<0.05). All the patients felt a different degree of pain on both sides during laser treatment, which was described as tingling sensation. Minor pain experience and better patient acceptance were reported in the Q-PTP laser mode treatment side. Q-PTP laser mode was significantly superior to single-pulse laser mode in procedural pain assessment and skin erythema assessment (Fig. 2).

Post-treatment skin erythema assessment was performed using a clinical assessment scale by two assessors. Results in each side treated with QS 1064-nm Q-PTP and single-pulse laser mode, respectively, were none (2 vs. 0), mild (8 vs. 5), moderate (2 vs. 6), and severe (0 vs. 1) (Fig. 2B). There was a statistically significant difference (P<0.05). Compared with before treatment (Fig. 3A-C), lesser skin erythema was observed in Q-PTP laser mode treatment after the treatment (Figs. 3D-F and 4).

Modified melasma area and severity index (mMASI). The mean mMASI score of each side of the face showed improvement after the final laser treatment at the 4th and 12th-week

Figure 3. A 45-year-old female patient whose right-side of the face was treated with QS 1064-nm Q-PTP laser mode and left-side was treated with single-pulse. (A) The patient's right face before treatment; (B) the patient's face before treatment; (C) the patient's left side face before treatment. The patient whose right-side face (D) was treated with QS 1064-nm Q-PTP laser mode, slighter skin erythema reaction was observed than the left-side (F), which was treated with single-pulse laser mode, under the same treatment parameters immediately after laser treatment. After the treatment, the right-side face (D) shows obvious improvements compared with the left side face (F). Effects of the two treatment methods are shown (E). Q-PTP, quickly-pulse-to-pulse.

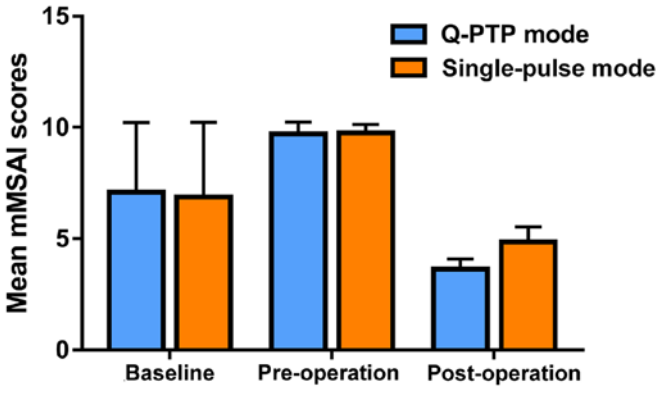

Figure 4. Data comparison chart of a 45-year-old female patient before and after treatment. Q-PTP, quickly-pulse-to-pulse.

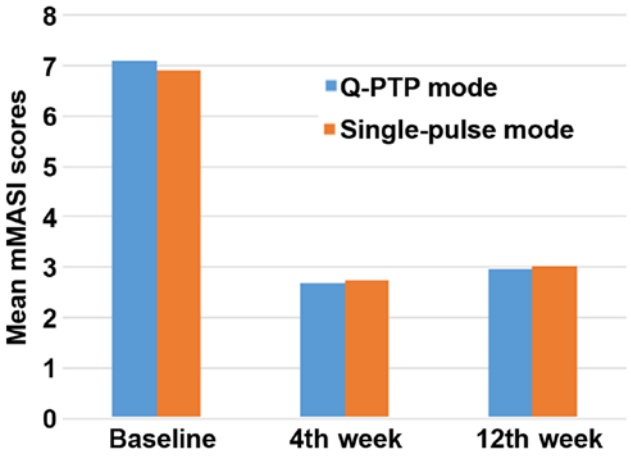

Figure 5. Mean modified MASI scores. The changes in the modified melasma area and severity index (mMASI) scores at baseline, at the 4th and 12th week follow-up. mMASI scores decreased significantly as compared to the baseline on both sides (both significant vs. baseline, P<0.05). Q-PTP, quickly-pulse-to-pulse.

follow-up visit compared to baseline (Fig. 5). Baseline mMASI scores were 7.09±3.13 on the side of the the face treated with Q-PTP mode and 6.89±3.35 on the other side treated with single-pulsed mode. There was no significant difference between the two sides (P>0.05). At the 4th week of follow-up, the mMASI scores were changed to 2.69±2.32 on the Q-PTP side and 2.75±2.38 on the single-pulsed side. mMASI scores were 2.97±2.52 and 3.03±2.37 on the Q-PTP and single-pulsed side, respectively, at the 12th week of follow-up. The mMASI score was 3 when the melasma lesion clearance was 50%.

Figure 6. A 42-year-old female patient whose right side of the face was treated with QS 1064-nm Q-PTP laser mode and the left side was treated with single-pulse. Melasma improvements were observed after five treatment sessions at the 4th week of follow-up (D-F), and both sides of the face showed a similar therapeutic effect. (Baseline A-C). Q-PTP, quickly-pulse-to-pulse.

In our study, 7 out of 12 patients had mMASI scores of less than 3. Mean mMASI scores were decreased significantly, as compared to the baseline on both sides ($P<0.05$). However, the difference in mMASI scores between the two laser modes was not statistically significant ($P>0.05$).

Physician's global assessment and Patients' self-assessment. QS 1064-nm Q-PTP and single-pulse laser mode were used to treat each half-face group, melasma improvement showed a positive treatment efficacy at the 4th week follow-up, compared with pre-treatment baseline (Figs. 6 and 7). The patient's satisfaction was good. However, both sides of the same patient showed similar therapeutic effect, with no statistical significance ($P>0.05$).

In PGA, improvement of melasma treated with Q-PTP and single-pulse laser mode was as follows: excellent (3 vs. 2); good (4 vs. 5); moderate (3 vs. 3); minimal (2 vs. 2); unchanged (0 vs. 0); worsening (0 vs. 0). Patients' self-assessment was as follows: excellent (4 vs. 4); good (3 vs. 3); moderate (4 vs. 3); minimal (1 vs. 2); unchanged (0 vs. 0); worsening (0 vs. 0) (Fig. 2C and D).

Adverse effects and recurrence. One patient (approximately 8.33%) who was treated with QS 1064-nm single-pulse modes experienced edema like acute urticaria (wheal), little visible petechiae and severe skin erythema for 24 h without specific treatment. Other serious complications such as hyperpigmentation, hypopigmentation or punctate leucoderma were not found in any other patient during the treatment, except for tingling sensation and slight burning which disappeared after a cooling collagen-containing mask was applied for 20 min. Mild to moderate skin erythema in our study was observed after the treatment session and disappeared in less than 2 h. Three patients (25%) had a relapse of the disease at the 12th-week follow-up visit.

Discussion

Melasma has a significant negative impact on the quality of life because it is a refractory disease of pigmentation disorders. Although there are still many challenges in the treatment of melasma, some studies have shown efficacy of laser and light therapy in the treatment of the disease (11-16). Using Q-switched lasers for treating pigmentation disorders is based on the theory of selective photothermolysis. The therapy technique 'laser toning' is based on subcellular selective photothermolysis (7,8) and its mechanism of action in melasma remains unclear. Although the technique removed melanosomes without damaging melanocytes, defects have been reported in the treatment of melasma in recent literature (17-19).

Figure 7. A 43-year-old female patient whose right side of the face was treated with QS 1064-nm Q-PTP laser mode and the left side was treated with single-pulse. Melasma improvements were observed after five treatment sessions at the 4th week of follow-up (A-C), and both sides of the face showed a similar therapeutic effect. (Baseline D-F). Q-PTP, quickly-pulse-to-pulse.

In order to eliminate the disadvantages and risks in the treatment of melasma, few side effects and good results of new laser technology or treatment schedule are being explored (20-23). Close attention should be paid to how to realize the balance of 'thermal control' to fit the target tissue in the laser and light treatment of melasma. The therapy with minimal thermal damage to melanocytes, achieves rapid elimination and metabolism rebalancing of melanin. QS Nd:YAG laser, fractional-mode and PTP laser technology as innovation was reported in recent studies. Q-PTP is the latest dual-pulse mode QS Nd:YAG lasers technology in which one pulse is split into successive two sub-pulses by very short intervals (80 μsec, in our study) and two relatively weak energy pulses are accumulated from photoacoustic to photothermal to produce higher peak power than those produced by the current QS single-pulse. Synergistic dual-pulse immediately led to pressure changes and vibration of melanin, and peak energy was accumulated to increase the temperature of the targets (20). Kim *et al* (24) conducted a study on the efficacy of the QS 1064-nm Nd:YAG laser and found the shock-wave effect of photoacoustic effectively destroys the melanin particles with less thermal damage.

In this study, QS 1064-nm Nd:YAG laser Q-PTP and single-pulse mode were used to treat each half-face of the patients. Melasma improvement showed treatment efficacy at the 4th week of follow-up, more than 50% of patients had higher lesion clearance compared with pre-treatment baseline. The patient's satisfaction was good. No serious complications were found in any of the patients during or after treatment. From baseline to the 4th week of follow-up after the final laser treatment, the mean mMASI scores showed a 62% reduction for the side of the face treated with Q-PTP mode vs. a 60% reduction for the single-pulsed mode. This difference in mMASI scores between the two laser modes was not statistically significant. In the 12th week of follow-up after the final laser treatment, there was a slight increase in mean mMASI for both sides. However, similar to the results at the 4th week of follow-up, both sides of the face still had a significant improvement from baseline. At a histological level, Fontana-Masson staining of the human skin revealed a similar effect of pigment destruction across the same parameters used in both modes of the QS 1064-nm Nd:YAG laser (24). In our study, the modified melasma area and severity index (mMASI) scores were used to quantify pigmentation changes in each side of the face.

Moreover, close attention was paid to procedural pain and post-treatment skin erythema reaction. From the feedback of the patients who had moderate to excellent improvement, we were pleased to find that their facial skin tone became healthier and brighter, and facial skin became smoother with better improvement of pores and fine wrinkles, possibly result of the increased type III collagen levels (24). Similar to our findings,

Jang *et al* (21) found that dual-pulsed and single-pulsed 1064-nm QSNY laser modes improved melasma significantly but modified MASI score, and L value (the value of brightness in the CIELAB color system) was not significantly different. Lesser pain and shorter duration of post-laser erythema were observed with the dual-pulsed mode. Compared to the single-pulsed laser mode, fewer side effects combined with similar efficacy may lead to Q-PTP being the preferred choice, especially pain sensitive skin types in patients with melasma or pain sensitive parts of the face such as periorbital treatment. Kim *et al* (24) observed by electron microscopy that dual-pulsed mode exhibited gentle treatment delivery on the basis of less epidermal keratinocytes and melanocytes damage. The relative lower expression levels of protease-activated receptors-2, pro-inflammatory transcription factors and pro-inflammatory cytokines were found in dual-pulsed mode compared to the conventional mode. High expression of the factors would cause skin erythema/inflammation or result to dyspigmentation.

Our study was conducted in southern China, although patients were required to use uniform sunscreen and given guidance on avoiding sunlight exposure, the patients' individual differences inevitably affected the treatment outcome. Three patients had a relapse of the disease at the 12th week of follow-up. However, there was no significant difference on either side of the face. We believe that a larger sample would be needed to analyze the recurrence of melasma. One patient suffered a relapse due to a severe facial allergy for nine weeks after laser surgery, one case was the result of sun exposure with outdoor working environment, and one may be due to the daily bad skin care habits causing skin rubbing damage. In our clinical practice, we found that epidemiological changes in the etiology of melasma. Improper skin care and the use of cosmetics lead to skin barrier damage, and adversely affect the occurrence and development of melasma. Impaired stratum corneum integrity and a delayed barrier recovery rate in melasma skin were reported by Lee *et al* (25).

The current treatment of melasma is still a comprehensive treatment and sequential treatment, and treatment schedule is adjusted according to the different conditions of the skin lesions. For the purpose of a comparative study, a laser monotherapy to treat melasma was applied. The number of research samples is small and the follow-up time is short, which are the limitations of our study. From the view of improving psychological condition through rapid reduction of pigment lesions, laser therapy is an indispensable treatment method as part of a comprehensive treatment program.

In conclusion, current laser physics technology and treatment strategy in laser therapy of melasma were explored. As a new technology of QS Nd:YAG laser, Q-PTP is a technical optimization of laser therapy in the treatment of melasma. Although there was no significant difference in the treatment outcome with the same treatment parameters, a minor procedural pain experience, lesser skin erythema reaction post-treatment and better patient acceptance demonstrate greater treatment safety and superiority than the current QSNY laser.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

XG conceived and designed the study and provided statistical methods. XC and YJ worked on laser treatment and post-treatment assessment. TZ and BW were responsible for physician's global assessment. QL helped with safety assessment. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Zhongshan Second People's Hospital (Zhongshan, China). Patients who participated in this research, had complete clinical data. Signed informed consents were obtained from the patients or the guardians.

Patient consent for publication

The patients provided consent for the data to be published.

Competing interests

The authors declare that they have no competing interests.

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