Lasers in Medical Science
https://doi.org/10.1007/s10103-019-02814-4

ORIGINAL ARTICLE

Low-fluence Q-switched Nd:YAG 1064-nm laser versus Q-switched Nd:YAG 532-nm laser in the treatment of hyperpigmented lips: a prospective, randomized, controlled, evaluator-blinded trial

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Received: 22 May 2018 / Accepted: 22 May 2019

Abstract
Lip hyperpigmentation is an esthetic problem. Clinical data from controlled comparative studies is insufficient to support the efficacy of laser treatments for hyperpigmented lips. This study is aimed to compare the efficacy of low-fluence Q-switched Nd:YAG 1064-nm laser (LFQS 1064-nm) versus Q-switched Nd:YAG 532-nm laser (QS 532-nm) for the treatment of hyperpigmented lips. A randomized, controlled, evaluator-blinded study was conducted in thirty subjects. They were randomized into 2 groups. The first group was treated with five treatment sessions with a 2-week interval of LFQS 1064-nm laser while the second group was treated with a single session of QS 532-nm laser. The evaluation was conducted at baseline, 2 weeks of each post treatment, and 4 weeks after the last treatment session. The efficacy was assessed by melanin index, Methuen colored plate, photographic evaluation, pain score, patient's satisfaction, and patient's Dermatology Life Quality Index. The adverse effects were also recorded. All patients attained throughout the study protocol. The most frequent fluence applied was 2.4 J/cm^2 (2.2–2.5 J/cm^2) and 2.0 J/cm^2 (1.7–2.4 J/cm^2) in the LFQS 1064-nm group and QS 532-nm group, respectively. The results of the QS 532-nm group showed greater percentage of melanin index reduction and better average mean of photographic evaluation percentage changes from the baseline than the LFQS 1064-nm group ($p < 0.001$ and $p < 0.001$, respectively). The adverse effects were less likely to occur in the LFQS 1064-nm group. Few cases of scale, hypopigmentation, bleb formation, postinflammatory hyperpigmentation, and labial edema occurred only in the QS 532-nm group.

Keywords Q-switched Nd:YAG 532-nm · Low-fluence Q-switched Nd:YAG 1064-nm · Melanin index · Hyperpigmented lips

Introduction

Lip hyperpigmentation is an esthetic concerned problem and has a negative impact on self-esteem [1]. The prevalence of this condition has not been documented yet. The diagnosis of hyperpigmentation is made by the clinical of diffuse, moderate dark-hued islands interspersed on the surface of the lip, excluding vascular lesions which are colored red, blue, or purple [2].

Concerning the treatment of this condition, there are some successful laser treatments reported for labial hyperpigmentation. QS 532-nm was used to treat Laugier-Hunziker syndrome (LHS) for both mucosal and cutaneous lesion with very satisfactory results; however, the new lesions came back 3 months after [3]. It was also used for labial lentigines associated with Peutz-Jeghers syndrome (PJS) which shown that after 2–6 treatment sessions, 72.7% of patients showed more than 75% lesion clearance. However, temporary adverse reactions occurred for almost 2 weeks [4]. Moreover, it was also used to treat dark lip from varying causes, all patients have complete clearance of the lesions after an average of 2.1 treatment session with 1 patient developed HSV labialis 3 days after the treatment [5].

Labial lentigines in PJS were also treated with Q-switched Ruby 694-nm with excellent results and no recurrence for at least 12 months of follow-up. The adverse events were just transient [6–8]. In addition, Q-switched alexandrite 755-nm was used to treat labial lentigines associated with PJS and LHS with mostly 100% clearance of lesions; however, a few cases recurred after 1 year of follow-up. The side effects

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Published online: 08 June 2019

included purpura for 3 days, crust formed then sloughed within 4–7 days [9–12]. There was a case report of using a Diode 940-nm laser to treat hyperpigmentation of lips as well. As the result, it can reduce the lip tone to be lighter within 7 days after treatment; nevertheless, most patients encountered the crusted lip for almost a week. [13].

As mentioned previously, the application of these lasers gave not only the most favorable outcome but also a number of undesirable side effects. Most patients usually complain of mild to moderate lip swelling, burning sensation, thin dry crust formation, minimal bleeding, and purpura after the treatment [5, 13]. However, using the low-fluence Q-switched Nd:YAG 1064-nm showed to have a fair result with only minimal side effects [14].

Nowadays, there is no standard laser treatment for lip hyperpigmentation. Those previous studies were only case reports and retrospective studies. As a result, we conducted a randomized, controlled trial comparing low-fluence Q-switched Nd:YAG 1064-nm (LFQS 1064-nm) and Q-switched Nd:YAG 532-nm (QS 532-nm) for the treatment of pigmented lips in Thai population.

Materials and methods

Study design

This study was an experimental, prospective, randomized, controlled, evaluator-blinded study. The number of subjects was calculated by PS sample size program (version 3.0), according to the previous study of Ostovari et al. [15]. Finally, 30 patients with diffuse pigmented lip were enrolled. Afterward, all study subjects were informed about the study procedures, risks, benefits, and potential side effects. The informed consent had been obtained and demographic data was recorded. The computer-generated block randomization was used to equally allocate patients to receive either LFQS 1064-nm laser or QS 532-nm laser. Our study was conducted at a university-based dermatologic clinic (Srinakharinwirot University, Bangkok, Thailand) from January 8, 2018, to April 6, 2018.

Inclusion criteria

The subjects are those aged over 20 years old with idiopathic hyperpigmented lip. The appearance of the lip is diffuse, moderate dark-hued islands interspersed on the surface without other systemic involvement which was assessed by history taking and physical examination. The pigmented area of lip had at least two darker scale comparing with the mucosal colored area, measured by Methuen colored plate.

Exclusion criteria

Patients who had a focal hyperpigmented lesion on the lips including labial melanotic macule, simple lentigines, solar lentigines, melanocytic nevus, pigmented seborrheic keratosis, pigmented Bowen' s disease, squamous cell carcinoma, and melanoma. Patients who had multiple diffuse hyperpigmented lesions on the lips and/or systemic involvement consisting of lentiginosis syndrome (e.g., Peutz-Jeghers syndrome, Bandler syndrome, LEOPARD syndrome, Carney complex, centrofacial lentiginosis, inherited patterned lentiginosis), endocrine and metabolic disorders (e.g., Addison's disease, Cushing's disease, hyperthyroidism, hemochromatosis, Nelson's syndrome, and acromegaly), heavy metal toxicities, and HIV infection. Patients who recently underwent lip tattooing or lip augmentation less than 2 years. Patients who had history of herpes labialis. Patients who are pregnant, which pregnancy test was done in all women cases. Patients who are breastfeeding. Patients who has an active lesion on the lips. Patients who are unable to follow up according to the study protocol.

Treatment protocol

The laser system employed in this study was Q-Switched Nd:YAG (MedLite C6; HOYA ConBio, Fremont, CA, USA). The laser unit emits dual wavelengths of 532-nm and 1064-nm with the maximum fluence of invisible beam of 1064-nm, 3.5 J/cm^2, 6-mm spot size, and 5.6 J/cm^2 for a 532-nm green light at 3-mm spot size. Topical anesthetic cream containing 5% lidocaine-prilocaine was applied to the entire lip, then occluded with the plastic wrap 30 min before every treatment. For the LFQS 1064-nm group, the patients received five treatment sessions with a 2-week interval. The settings were 6-mm spot size with 5 Hz of frequency and the most frequent fluence applied was 2.4 J/cm^2 (range 2.2–2.5 J/cm^2). In the QS 532-nm group, a single-session laser treatment was performed. The settings were 3-mm spot size at a frequency of 1 Hz and the mean fluence employed was 2 J/cm^2 (range 1.7–2.4 J/cm^2).

The clinical endpoint was defined as mild erythema without petechiae for LFQS 1064-nm laser and immediate whitening for QS 532-nm laser. Postoperatively, patients were given petrolatum ointment to apply topically on the lip at least 3 times per day for at least 7 days and were instructed to avoid using lipstick and sun exposure for at least 2 weeks. Follow-up and evaluation was scheduled at a 2-week interval after each laser treatment and 4 weeks after the last laser treatment for both groups. Therefore, the total study time was 4 and 12 weeks for the QS 532-nm group and LFQS 1064-nm group, respectively (Fig. 1).

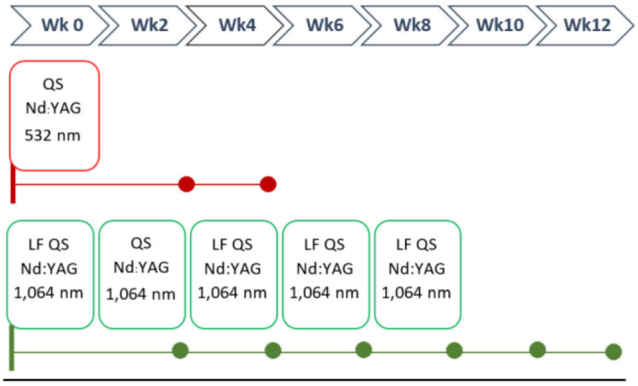

Fig. 1 Timeline of study protocol of the LFQS 1064-nm group and QS 532-nm group

Outcome evaluation

The clinical outcomes were evaluated for melanin index by using Mexameter MX16® (Courage + Khazaka Electronic, Cologne, Germany), photographic evaluation appraising by two dermatologists and the change of lip color by using the Methuen colored plate. The Methuen colored plate was created from Art Quill Studio which constructed a knowledge base in order to develop ArtCloth [16]. These thirty-six shades of red color have been graded tonally in columns by overprinting with transparent gray inks and increasing deep tone to the basic red color of each row (Fig.2). The Methuen colored plate score was assessed by the number of scale changed from baseline at the darkest area, then categorized either in 1-scale better group, 1-scale worsen group, or no changing scale group, reported in percentage.

The patient's satisfaction to study's result was assessed by using a visual analog scale. The patient's Dermatology Life Quality Index (DLQI) was evaluated by using Thai DLQI version. Pain score was rated by a 10-point pain scale according to Wong-Baker Faces Pain Rating Scale at the first laser treatment of each group. The adverse effects as well as their duration and intensity were recorded at each visit. The intensity was graded as 0 = no side effect, 1 = mild intensity, 2 = moderate intensity, and 3 = severe intensity.

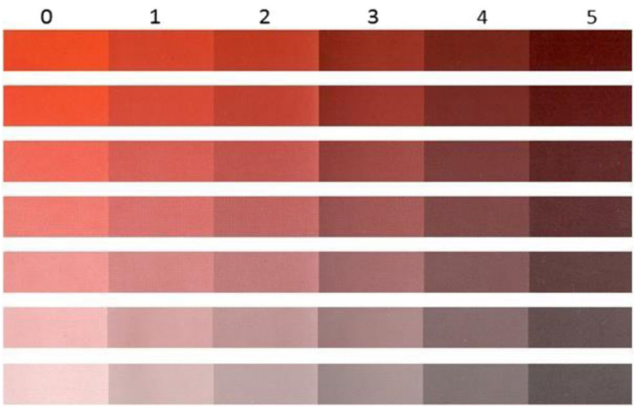

Fig. 2 The grading of Methuen colored plate

Statistical analysis

Categorical variables of baseline characteristics were analyzed as frequency and percentage, whereas the continuous variables were analyzed as mean ± standard deviation or median ± interquartile range. For the inferential statistics, the Kolmogorov-Smirnov test or Shapiro-Wilk W test was used to test the distribution of the data, if the data was a normal distribution, an independent *t* test was used to compare the average mean for continuous data between two independent samples while the paired *t* test was used to compare the average mean for the dependent one. However, if the data was non-normal distribution, the Mann-Whitney *U* test and Wilcoxon signed rank test would be applied to compare two independent samples and the dependent one, respectively. Pearson's chi-square was used to determine the difference for categorical data. The statistical analysis was performed by using STATA version 13 (Stata Corp., College Station, Texas, USA). A *p* value of 0.05 or less was considered statistically significant.

Results

Demographic data

All subjects with idiopathic hyperpigmented lip have completely attained the study protocol. Twenty-two (73.33%) patients were female and eight (26.67%) were male. The mean age of LFQS 1064-nm and QS 532-nm group was 27.13 ± 7.23 and 28.33 ± 8.49, respectively. The etiologies for hyperpigmented lips were physiologic pigmentation, smoking, and postinflammatory hyperpigmentation due to lipstick allergy. The baseline of melanin index and Methuen colored plate of the reddest and the darkest areas was recorded. The baseline of DLQI score was also recorded. There was no significant difference of all parameters detected between the two groups (Table 1).

Outcomes

The picture of the clinical outcomes of QS 532-nm laser at week 4 and LFQS 1064-nm laser at week 12 comparing with the baseline is shown in Fig. 3. The results of all the outcomes from baseline to 4 weeks after the last treatment of each group are shown in Table 2.

Regarding the melanin index, it was demonstrated that the melanin index of both groups was lower than the baseline. However, the melanin index percentage changes reduction from baseline shown that the QS 532-nm group was greater than the LFQS 1064-nm group with statistically significant difference ($p < 0.001$).

For the Methuen colored plate evaluation, it was shown that all subjects in LFQS 1064-nm group demonstrated no

Table 1 Demographic data

Demographic data	LFQS 1064-nm group ($n = 15$)	QS 532-nm group ($n = 15$)	p value
Female, n (%)	12 (80)	10 (66.67)	0.41
Male, n (%)	3 (20)	5 (33.33)	0.68
Mean age (years ± SD) (range)	27.13 ± 7.23 (20–49)	28.33 ± 8.49 (20–49)	0.68
Etiologies of dark lips			
- Physiologic pigmentation, n (%)	10 (66.67)	8 (53.33)	0.55
- Smoking, n (%)	2 (13.33)	1 (6.67)	
- Postinflammatory hyperpigmentation, n (%)	3 (20)	6 (40)	
Mean melanin index of the reddest area (SD)	454.05 (6.70)	450.11 (7.59)	0.143
Mean melanin index of the darkest area (SD)	511.01 (17.75)	519.22 (28.39)	0.350
Methuen plate 10 scale of the reddest area			
- Level 0. n (%)	0 (0)	0 (0)	0.341
- Level 1, n (%)	0 (0)	2 (13.33)	
- Level 2, n (%)	14 (92.33)	12 (80)	
- Level 3, n (%)	1 (6.67)	1 (6.67)	
- Level 4, n (%)	0 (0)	0 (0)	
- Level 5, n (%)	0 (0)	0 (0)	
Methuen plate 10 scale of the darkest area			
- Level 0, n (%)	0 (0)	0 (0)	0.222
- Level 1, n (%)	0 (0)	0 (0)	
- Level 2, n (%)	0 (0)	0 (0)	
- Level 3, n (%)	0 (0)	1 (6.67)	
- Level 4, n (%)	13 (86.67)	9 (60)	
- Level 5, n (%)	2 (13.33)	5 (33.33)	
Mean DLQI (SD)	8.87 (3.85)	9.27 (4.18)	0.787

change in scale evaluation, whereas, there was 6.7% of 1-scale worsen, 20% of 1-scale better, and 73.33% of no changing scale in the QS 532-nm group. However, no significant difference between two laser groups was detected ($p = 0.539$).

Concerning the photographic assessment, it was demonstrated that the QS 532-nm group had 40.17% improvement at the end of the study, in spite of only 5% improvement in the LFQS 1064 group with statistically significant difference ($p < 0.001$).

As regards to the patient's satisfaction and the patient's DLQI score, it was found that the QS 532-nm group had a higher satisfaction score and DLQI score reduction comparing with the LFQS 1064-nm group with statistical significant difference ($p < 0.001$ and $p = 0.04$). Regarding pain score evaluation, the QS 532-nm group encountered more pain than the LFQS 1064-nm group ($p < 0.001$).

The adverse effects have shown that burning sensation, itching, and dryness developed in both groups.

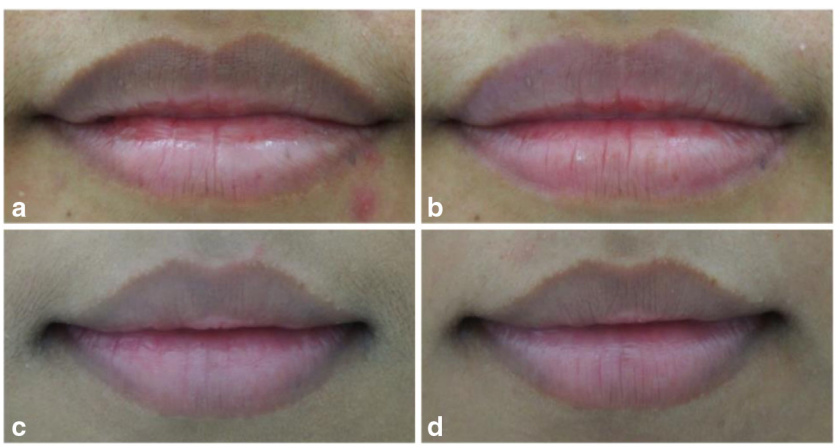

Fig. 3 The clinical picture of hyperpigmented lip at baseline and the end of study in QS 532-nm group (**a**, **b**) and LFQS 1064-nm group (**c**, **d**)

Table 2 Comparison of the outcomes from the baseline to 4 weeks after the last treatment between LFQS 1064-nm and QS 532-nm group

Outcome data	LFQS 1064-nm group ($n = 15$)	QS 532-nm group ($n = 15$)	p value
Mean, % change of melanin index (SD)	− 1.6 (0.21)	− 4.8 (2.21)	< 0.001
Mean, % change of Methuen colored plate			
- 1-scale worsen, n (%)	0 (0)	1 (6.67)	0.539
- No change, n (%)	15 (100)	11 (73.33)	
- 1-scale better, n (%)	0 (0)	3 (20)	
Mean, % change of photograph (SD)	5 (4.12)	40.17 (21.29)	< 0.001
Mean, patient's satisfaction score (SD)	0.53 (0.52)	1.73 (0.46)	< 0.001
Mean, change of DLQI score (SD)	− 4.53 (2.03)	− 6.93 (3.75)	0.041
Mean, pain score (SD)	1.67 (0.98)	5.07 (1.03)	< 0.001

Burning sensation was the only side effect that had essential higher significant incidence in the QS 532-nm group ($p < 0.001$), whereas itching and dryness had no difference between the two groups ($p = 0.14$ and $p = 0.39$). Scale, bleb formation, postinflammatory hyperpigmentation, hypopigmentation, and labial edema occurred only in the QS 532-nm group (Fig. 4). The longest duration among all the adverse events was hypopigmentation (14.71 ± 3.20 days). Most of hypopigmentation was detected obviously immediately after the sloughing of scale (approximately day 5 or 6 after laser treatment) and gradually regained pigment within 2 weeks. No permanent hypopigmentation was detected. The greatest intensity of the occurring side effect was scale formation (1.38 ± 0.43). Most scale began to form at day 1 or 2 after the QS 532-nm laser treatment and sloughed around 3 days afterward. None of the subjects reported the difficulty in eating or moving the lips during the scale formation. Postinflammatory hyperpigmentation (PIH) occurred in one patient in the QS 532-nm group. Therefore, 2% hydroquinone gel was prescribed and the PIH resolved completely within 2 weeks.

Discussion

Lip hyperpigmentation is a cosmetic and psychologically distressing pigmentary condition. There are many associated factors contributing to this condition. The clinical manifestations of pigmented lips are diverse, depending on the underlying etiologies. Histological findings of lip darkening demonstrate aberrant aggregation of melanin granules in the basal layer with a regular number of melanocytes and excessive dermal melanophages [5], which serve as excellent targets for Q-switched laser that have melanin as a chromophore.

There is a paucity of literature regarding the treatment of lip hyperpigmentation. In 2001, Kunachak et al. [5] performed a retrospective study about treating homogenous diffuse dark lips in 72 Thai patients by using a QS 532-nm laser. To the best of our knowledge, there is no randomized controlled trial about the laser treatment for hyperpigmented lips. The present study is the first randomized controlled trial to determine an efficacy of both LFQS 1064-nm and QS 532-nm for the treatment of hyperpigmented lips.

The subjects presented in this study have similar characteristics with the previous publication which their etiologies consisting of physiologic pigmentation, smoking, and

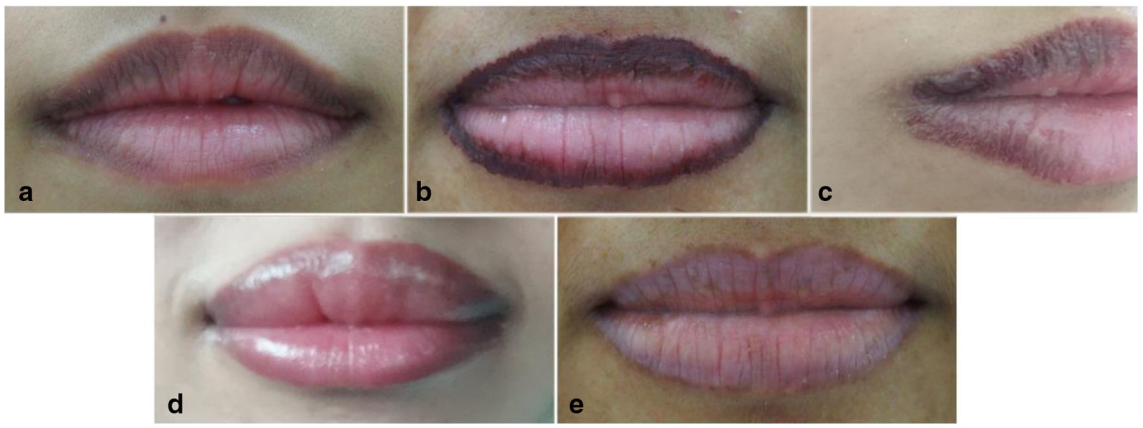

Fig. 4 Photographs of the side effects occurred in QS 532-nm group including postinflammatory hyperpigmentation (**a**), scale formation (**b**), bleb formation (**c**), labial edema (**d**), and hypopigmentation (**e**)

postinflammatory hyperpigmentation. Concerning the subjective measurements, it was found that all the parameters except the Methuen colored plate were better than baseline with statistical difference in both groups. In addition, the QS 532-nm groups showed greater results than LFQS 1064-nm group with statistically significant difference. Regarding the objective measurement, it was shown that the melanin index was decreased in both groups; however, the QS 532-nm group showed statistical significant greater percentage changes melanin index reduction than LFQS 1064-nm group. For the subject's evaluation, it was found that both satisfaction score and DLQI score in QS 532-nm group were statistical significant higher than LFQS 1064-nm group.

Regarding the mechanism of Q-Switched Nd:YAG laser, it could be simplified that the destructive effect of Q-Switched Nd:YAG laser on epidermal melanosomes and pigmentary incontinence can result in darkness reduction of the lip in the treated subjects. According to the depth of optical penetration, the wavelength of 532-nm is only effective on superficial pigment and does not have deep penetration like 694-nm and 755-nm, which both wavelengths can penetrate to mid-dermis, and 1064-nm which can penetrate to the deep-dermis [17]. However, the 1064-nm wavelength has lower absorption coefficient of melanin than 532-nm wavelength, thus, the efficacy of the 532-nm is greater for treatment of hyperpigmentation [17, 18]. Moreover, the dermo-epidermal and upper dermal location of labial melanin deposition could explain the better efficacy of the QS 532-nm laser in comparison with the LFQS 1064-nm laser, which is basically more effective in the mid-dermal pigmentation.

The adverse effects were less likely to occur in the LFQS 1064-nm group. Lesser intensity and shorter duration were also observed in the LFQS 1064-nm group. This was probably due to the depth of penetration of laser energy varies according to wavelength, such 532-nm acts more superficially and much more highly absorbed into melanin whereas 1064-nm can penetrate the deeper dermis and lesser specificity [18]. In this fashion, there are more adverse effects and the risk of dyspigmentation is significantly higher in QS 532-nm. However, there were some reports about multiple treatments of LFQS 1064-nm for the treatment of melasma that could end up with permanent confetti-like hypopigmentation [19–21]. Nevertheless, in this study, we observed no serious/permanent complication except one patient who had postinflammatory hyperpigmentation in QS 532-nm group which completely resolved after using 2% hydroquinone gel.

According to the pain evaluation, the QS 532-mm group had a significantly higher score, although all patients were well-tolerated to the treatment. This result was possibly due to more reactions that were created during QS 532-nm treatment because most laser-targeted chromophores were scattered in the basal layer and upper dermis. Meanwhile, LFQS 1064-nm, also known as laser toning, could penetrate deeper and deliver subthreshold energy that causes less pain comparing with traditionally high fluence setting [22].

As for the patient's response evaluations, both groups showed better patient's satisfaction score and DLQI score but QS 532-nm groups had substantially greater improvement than LFQS 1064-nm group. However, these subjective scores may vary due to individual judgment and experience.

Our study is the first randomized, controlled trial of using QS 532-nm in the treatment of lip hyperpigmentation. Baseline demographics of both groups were equally balanced. The follow-up period was well-constructed with 2 and 4 weeks after the last treatment. Therefore, it was easier to detect any subtle changes of clinical outcome more delicately. The outcomes of this study have been evaluated for both subjective and objective measurement which their results are positively correlated. Moreover, this study has used the red color grading scale from the Methuen colored plate to assess the colored changes of the lips, which has never been applied in any trial before.

However, this study had limitations. Firstly, for baseline characteristic, only few etiologies of hyperpigmented lip were presented and female patients were predominated. As a result, the outcome may face limitations if inferred to patients with different etiologies or male patients. Secondly, the sample size is too small in each group. Thirdly, the follow-up period of both QS 532-nm and QS 1064-nm groups should be longer in order to see the further clinical outcome and the incidence of recurrent rate. Lastly, the Methuen colored plate changed from baseline was indifferent between the two groups which was probably due to the small number of subjects in each group. Future studies should investigate increasing the number of subjects and expanding the duration of follow-up period in the QS 532-nm group.

In conclusion, the QS 532-nm laser has shown to be more effective in the treatment of the hyperpigmented lips. However, more incidence, duration, and intensity of adverse effects comparing with the LFQS 1064-nm laser can be observed.

Acknowledgments We would like to thank the Faculty of Medicine, Srinakharinwirot University for providing the grant.

Compliance with ethical standards This study has been approved by the Clinical Research Ethical Committee of Srinakharinwirot University on December 27, 2017, Certificate No. SWUEC/E-286/2560. The study protocol followed the guidelines of the 1964 Helsinki declaration. All patients signed informed consent before participating in the study.

Conflict of interest The authors declare that they have no conflict of interest.

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