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A study of efficacy and safety of high-intensity focused ultrasound for the treatment of melasma in Asians: A single-blinded, randomized, split-face, pilot study

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ABSTRACT

Background: A recent report suggested potential of high-intensity focused ultrasound in improving UVB-induced hyperpigmentation in patients with Fitzpatrick skin type IV, but reports regarding its efficacy in other hyper-pigmented conditions including melasma are lacking.

Objectives: To investigate efficacy and safety of high-intensity focused ultrasound for the treatment of melasma in Asians.

Methods: Each side of the face of 25 melasma patients was randomized to receive 3-monthly sessions of high-intensity focused ultrasound treatment or serve as control. Lightness index, Melasma Area and Severity Index of malar area ($MASI_m$) by blinded dermatologists, self-evaluated improvement and satisfaction scales by patients, and side effects were assessed every 4 weeks for 20 weeks.

Results: Twenty-one patients with Fitzpatrick skin type III and IV completed the study. There was a greater reduction of relative lightness index and MASIm after treatment in high-intensity focused ultrasound-treated side. However, there were no statistically significant differences between both sides. More than 50% improvement on treatment side was rated in 11 patients (52.4%). Side effects were minimal. None had worsening of melasma.

Conclusion: High-intensity focused ultrasound may be an adjuvant for treatment of melasma. Further studies with larger sample size and proper parameter settings are recommended to determine its efficacy.

KEY WORDS: chloasma, hyperpigmentation, laser, melasma, pigmentary disorder

1. INTRODUCTION

Melasma is a common acquired pigmentary disorder seen worldwide especially in those living in ultraviolet-intense areas. It is characterized by light brown to dark, muddy brown macules, and patches on the face, typically on the forehead, malar prominences, and chin. In terms of pathogenesis, melasma is thought to be a result of the presence of functionally active melanocytes in the lesions rather than an increase in melanocyte number. To classify melasma by its locations, 3 clinical patterns have been described, namely a centro-facial pattern, which is the most common, a malar pattern, and a mandibular pattern. Although biologically benign, this condition has significant negative impact on patient's psychological health and quality of life.[1] Melasma is relatively difficult to deal with; however, it has been traditionally managed with a combination of photo-protection, avoidance of triggers, and topical medications with variable success rate. Laser therapy showed varying improvement and some reported a potential of worsening.[2] Therefore, newer topical agents, lasers, and energy-based devices have been introduced as promising options for treatment, particularly in difficult-to-treat patients.

High-intensity focused ultrasound (HIFU) has been utilized as a therapeutic device for the treatment of solid benign and malignant tumors.[3] In dermatological practice, it has been introduced as a non-invasive option for skin tightening and rejuvenation. The mechanism of HIFU involves delivery of high-frequency ultrasound underneath the skin and induction of precise thermal damage to specific depth under the skin. These then result in dermal collagen regeneration, and contraction of the superficial muscular aponeurotic

system without epidermal or adjacent tissue injury. Recently, Choi et al[4] demonstrated positive effects of HIFU in ultraviolet B-induced hyper-pigmentation in guinea pig skin by applying HIFU via a 1.5-mm transducer. They also proposed that HIFU has a mechanical destructive activity in eliminating melanin from the epidermis and upper dermis. According to a recent study, the efficacy and safety of HIFU for UVB-induced hyperpigmentation in human subjects with Fitzpatrick (FPT) skin type III or IV were demonstrated. The results revealed greater improvement in lightness index as well as in improvement score in participants with skin type IV compared to controls while HIFU showed inferior efficacy for both parameters in skin type III to controls.[5] To our knowledge, a clinical study regarding the efficacy and safety of HIFU in treating melasma has not been published in the literature. Therefore, we aim to determine the efficacy and safety of HIFU in the treatment of melasma, particularly in Asians.

2. MATERIALS AND METHODS

2.1 Study design

This is a split-face, evaluator-blinded, randomized controlled trial. The objective was to investigate the efficacy and safety of HIFU in the treatment of melasma. The study was approved by the Faculty of Medicine Ramathibodi Hospital Institutional Review Board of Human Rights Related to Research Involving Human Subjects, Mahidol University (protocol number 026026). The study protocol complied with the guidelines of the Declaration of Helsinki. Information on the study procedures, benefit, and potential risk was given to the patients before enrolling in the study. All patients provided informed consent before participating in the study.

2.2 Patients

Twenty-five participants aged over 18 years old with mixed-type melasma in both malar areas were recruited from the dermatology out-patient clinic at a university-based hospital (Ramathibodi Hospital, Mahidol University, Bangkok, Thailand). Participants were excluded if they had pregnancy or lactation, medical or dermatologic conditions including autoimmune disorders, scars, or severe cystic acne on the face, a history of photosensitive disorders, allergy to topical hydroquinone, or a previous history of the following treatments or procedures: oral contraceptive pills or hormone replacement therapy within 1 year, topical whitening agents within 3 months, laser treatment including HIFU treatment within 6 months, or filler injection on the experimental sites within 1 year.

2.3 Treatment and follow-up

All eligible participants were randomly allocated to

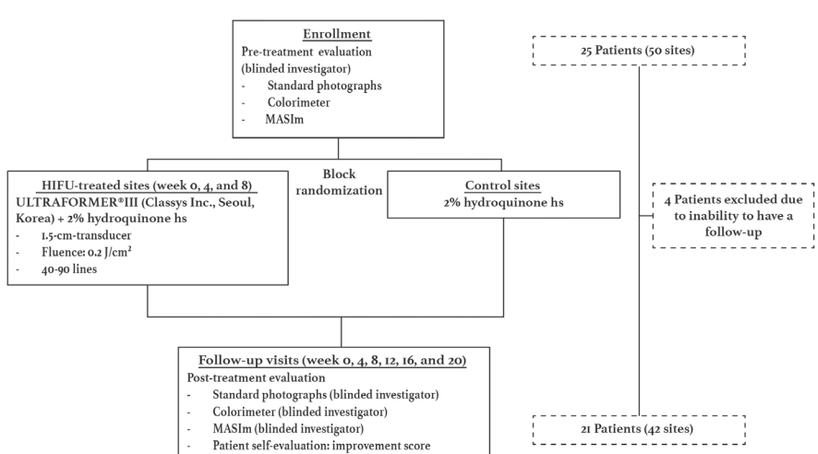

Figure 1 Protocol flowchart and number of the participants at baseline, number of excluded participants, and number of participants included in the statistical analyses

receive the treatment of HIFU on one side of the face based on a computer-generated random sequence, while the contralateral side served as control. The face was cleaned with a gentle cleanser before the treatment. Standard digital photographs (Visia CR, Canfield Imaging System) were taken from the front as well as both sides of the face. The HIFU treatment (ULTRAFORMER® III, Classys Inc) was performed with a fluence of 0.2 J/cm^2 via a 7-MHz, 1.5 mm transducer, fluence 0.2 J/cm2 in 3 consecutive sessions at baseline, 4th, and 8th week. Lubricating gel (K-Y Jelly™, Johnson & Johnson) was applied to the treated areas prior to HIFU therapy. Forty to ninety lines of HIFU were delivered without overlap in 2 passes, each with either a horizontal or vertical orientation, until the endpoint of mild erythema was seen. All participants were requested to apply a 2% hydroquinone gel bilaterally before bedtime as well as a broad-spectrum sunscreen with a sun protection factor (SPF) of 50+ and protection grade of UVA (PA) of more than eight (PA+++). They were also instructed to avoid direct sun exposure, concomitant use of any other topical medications, and vigorous rubbing on the treated areas during the study period. After the last treatment, the participants were followed up every 4 weeks for 3 times, giving a total of 6 visits. The study protocol is shown in Figure 1.

2.4 Outcome evaluation

Objective assessment was performed at each visit using colorimeter (DSM II ColorMeter®, Cortex Technology). Lightness index (L*I) was obtained by the average of three measurements taken from the darkest areas of melasma and from normal skin on both sides of the face. Reproducibility was achieved by using a transparent plastic map indicating the same measured target. The difference in L*I be-tween normal skin and lesion was calculated and represented as a relative lightness index RL*I.

Relative lightness index

(RL * I) = L * I of normal skin - L * I of melasma

The severity of melasma was also subjectively evaluated in terms of Melasma Area and Severity Index on the malar area ($MASI_m$) by 2-blinded dermatologists at baseline and every visit. $MASI_m$ was scored and calculated based on the following parameters: percentage of involvement or “A” ranging from 0 to 6 (0 = 0%, 1 = <10%, 2 = 10%-29%, 3 = 30%-49%, 4 = 50%-69%, 5 = 70%-89%, 6 = 90%-100%), darkness of pigment or “D” ranging from 0 to 4 (0 = absent or normal skin color without evidence of hyperpigmentation, 1 = slight visible hyperpigmentation, 2 = mild visible hyperpigmentation, 3 = marked hyperpigmentation, 4 = severe), and homogeneity or density of hyperpigmentation (number of pigmented lesions per unit facial area) or “H” ranging from 0 to 4 (0 = minimal, 1 = slight, 2 = mild, 3 = marked, 4 = severe).

$$MASI_m = (D+H)\times A$$

Characteristics	n = 21
Gender	
Male, n (%)	3 (14.3)
Female, n (%)	18 (85.7)
Age (y); mean (SD)	46.3 (7.7)
Fitzpatrick skin type	
Type III, n (%)	11 (52.4)
Type IV, n (%)	10 (47.6)
Disease duration (y); median (range)	6.5 (1-30)
Baseline R*LI	
HIFU-treated sites (mean ± SD)	7.19 ± 2.67
Control sites (mean ± SD)	7.66 ± 2.72
Baseline mMASI	
HIFU-treated sites (mean ± SD)	15.33 ± 5.91
Control sites (mean ± SD)	15.00 ± 6.19

TABLE 1 Demographic data and baseline R*LI and mMAS

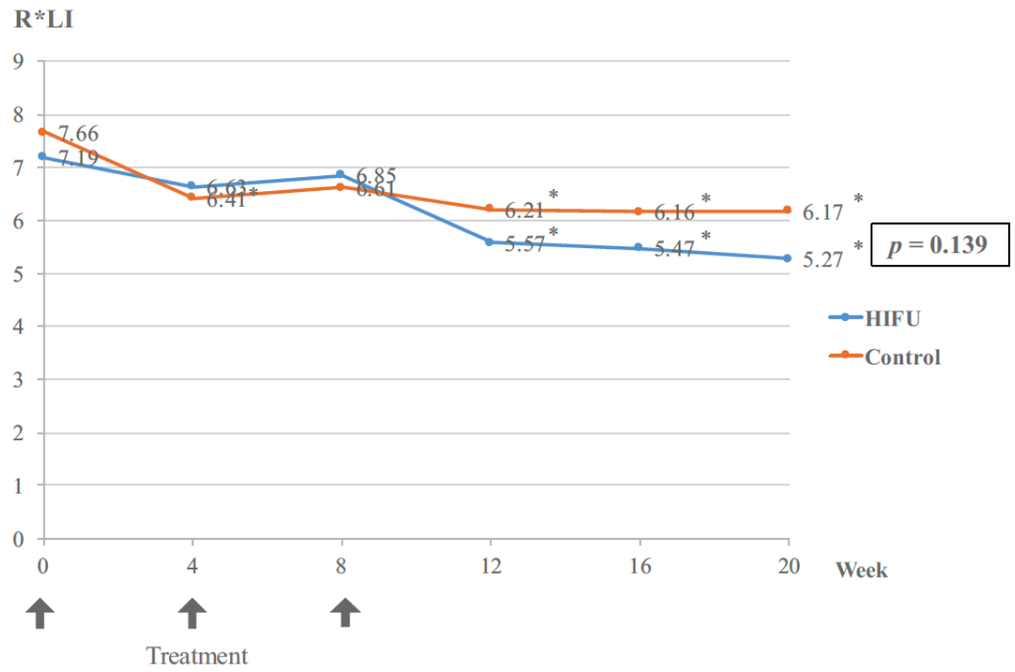

FIGURE 2 Mean relative lightness index (RL*I) of HIFU-treated side in comparison with control side (*significant reduction compared with baseline P < 0.05)

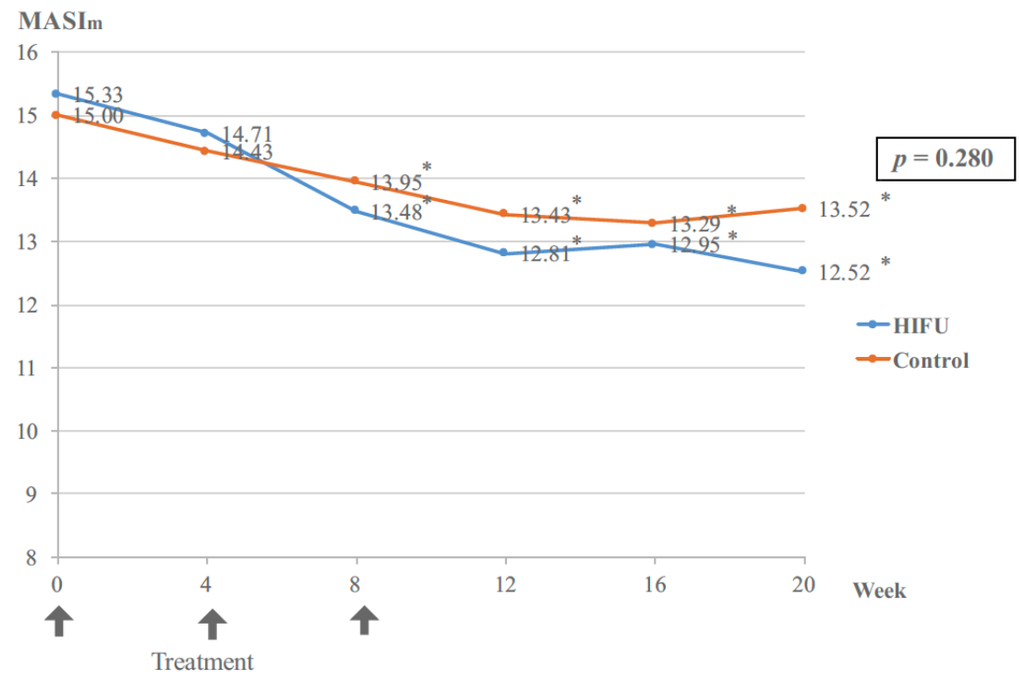

FIGURE 3 Mean Melasma Area and Severity Index of the malar area ($MASI_m$) of HIFU-treated side compared with control side (*significant reduction compared with baseline P < 0.05)P < 0.05)

At the 4th visit, improvement score was rated by participants according to the following scale: excellent = 90%-100% improvement, good = 60%-89% improvement, fair = 30%-59% improvement, poor = 0%-29% improvement, or worsening. Satisfaction score was also assessed in all participants by using a numerical scale, ranging from 0 point (very dissatisfied) to 10 points (very satisfied).

Regarding safety, pain score was also noted by using a numerical scale ranging from 0 to 10 with 0 as no pain and 10 as the most severe pain. Adverse effects were assessed by dermatologists at every visit.

2.5 Recurrence

At the final visit, recurrence which is defined as increment in RL*I or $MASI_m$ more than 50% from the 4th visit was assessed and reported in percentage.

2.6 Statistical analyses

Statistical analyses were performed using Stata/SE version 14.2 (StataCorp, College Station, TX). Categorical variables were presented as percentages while continuous variables (e.g. RL*I, $MASI_m$, pain score, satisfaction score) were presented in terms of mean ± standard deviation. Patient grading of improvement was calculated in percentage. The effects of treatment in terms of mean RL*I and mean MASIm, together with the effects of Fitzpatrick skin type, were determined using multilevel mixed-effects linear regression analysis. A P-value of 0.05 or less was considered statistically significant.

3. RESULTS

Demographic data are summarized in Table 1. Twenty-five patients were enrolled in the study. Four participants dropped out from the study after the 4th-week (1 patient), 8th-week (1 patient), 12th-week (1 patient), and 16th-week visit (1 patient) due to inability to follow-up. Twenty-one participants completed the protocol and were included in the statistical analyses. Eighteen participants were female (85.7%), while 3 participants were male (14.3%). Their age ranged from 30 to 56 years, with a mean of 46.3 years. Eleven participants had Fitzpatrick skin type III (52.4%), whereas 10 had skin type IV (47.6%). There were no statistically significant differences in terms of mean RL*I or mean $MASI_m$ between the HIFU-treated and control sides at baseline.

3.1 Color measurement

Mean RL*I at each visit is demonstrated in Figure 2. On the HIFU-treated side, the mean RL*I decreased from 7.19 ± 2.67 at baseline to 5.57 ± 2.91 at 4 weeks after the last HIFU treatment (12th week), accounting for 22.5% reduction. This decrease reached statistical significance (P = 0.006). Mean RL*I of the treated side was further slightly reduced to 5.47 ± 2.52 and 5.27 ± 2.7 at the 16th and 20th week, respectively (P = 0.004 and P = 0.001). Likewise, the mean RL*I of the control side significantly declined from 7.66 ± 0.47 to 6.21 ± 2.83 at the 4th visit, representing 18.9% reduction (P = 0.014) (Figure 2). The mean RL*I also significantly decreased from baseline to 6.16 ± 2.75 and 6.17 ± 3.74 at the 16th and 20th week (P = 0.011 and 0.012), respectively. There were no statistically significant differences in terms of overall mean RL*I between HIFU-treated and control sides (P = 0.139). There was no significant impact of different skin types on RL*I (P = 0.189).

3.2 $MASI_m$

The mean $MASI_m$ before treatment was 15.33 ± 5.91 and 13.43 ± 6.1 for the HIFU treated and control sides, respectively. After the HIFU treatment, there was a statistically significant decrease in MASIm to 12.81 ± 6.79 on the treated side (P < 0.001), accounting for 16.4% reduction. At the 16th and 20th week, there was also a significant reduction of mean $MASI_m$ to 12.95 ± 6.67 and 12.52 ± 6.91, respectively (P < 0.001). On the control side, the mean $MASI_m$ significantly reduced from 15.00 ± 6.19 to 13.43 ± 6.10, representing 10.5% reduction (P = 0.002) (Figure 3). The control side also showed a significant decline in $MASI_m$ to 13.29 ± 6.17 and to 13.52 ± 6.22 at the 15th and 20th week (P = 0.001 and 0.003, respectively). However, the overall differences of mean $MASI_m$ between the HIFU-treated and control sides did not reach the statistical significance level (P = 0.280) (Figure 3). Skin type did not appear to significantly affect $MASI_m$ in the present study (P = 0.408).

3.3 Patient self-assessment and satisfaction score

Ten participants (47.6%) rated improvement of melasma on the HIFU-treated side as "good" or "51%-75% improvement" (Table 2). One participants (4.8%) scored excellent improvement, while "fair" and "poor" were rated by 7 (33.3%) and 3 (14.3%), respectively. On the control side, most patients (14 patients, 66.7%) rated as "fair" and 5 patients (23.8%) rated as "poor." No patients on both groups reported worsening of melasma. The mean satisfaction score evaluated by the participants at the 4th visit was 6.62 ± 1.60, ranging from 4 to 10. Photographs of patients before and after treatment are shown in Figures 4 and 5.

3.4 Recurrence

Adhering to the definition of recurrence with more than 50% increase in RL*I or $MASI_m$, no case of recurrence was found at 3 months after the last treatment (Figures 2 and 3).

3.5 Safety assessment

The median pain score was 2 (range: 0-7). Side effects are listed in Table 3. One patient experienced burning sensation that subsided within 1-2 days without treatment. Two patients had adverse events from topical hydroquinone on both sides of the face including scaling (1 patient) and erythema (1 patient) which both spontaneously resolved without treatment or cessation of hydroquinone application (Table 3). No participants experienced PIH or worsening of melasma in this study.

4. DISCUSSION

Melasma is a common dermatologic condition that predominantly occurs in Fitzpatrick skin types III and IV.[1] Given its significant impact on patient's quality of life and psychological well-being, various treatment modalities including topical treatment, chemical peels, as well as laser and light treatment, have been described.[2] Nonetheless, dealing with melasma remains a problematic issue since topical treatment shows varying degrees of therapeutic success while laser therapy provides unpredictable improvement with potentials of worsening.[3] Seeking alternative options for melasma especially in recalcitrant or darkly pigmented patients is challenging.

High-intensity focused ultrasound is an innovative technology recently used in the management of skin laxity and rejuvenation. It delivers high-frequency ultrasound to specific layers of the skin and creates thermally induced contraction of collagen and tissue coagulation at the temperature up to 70°C while preserving the epidermis. This subsequently causes tissue repair cascade including collagenesis and elastogenesis that helps improve laxity in aging skin.[6,7] In 2015, Harris et al investigated HIFU application in 52 patients with skin types III to VI and proved that HIFU was safe and effective in darker-skinned patients without pigmentary adverse events.[8] Previous experimental study conducted by Choi et al reported potentials of HIFU in ultraviolet B (UVB)-induced hyperpigmentation using an animal model. HIFU irradiation with 1.5 cm depth transducer at 0.1 and 0.2 J/cm^2 was applied to UVB-induced hyper-pigmented areas of guinea pig skin.[4] Macroscopic improvement of pigmentation was observed at 2 weeks and at 3 weeks after HIFU with 0.2 J/cm^2 and with 0.1 J/cm^2, respectively. Reduction in UVB-induced melanin deposition was also seen in histopathology at 3 weeks after HIFU application. The proposed mechanism was mechanical destructive effects which play an important role in elimination of hyper-pigmentation. More recently, a study in humans suggested that HIFU may be offered in some patients with UVB-induced hyper-pigmentation. A superior efficacy of HIFU in the treatment of UV-

Improvement (%)	HIFU-treated side, n = 21 (%)	Control side, n = 21 (%)
Excellent (75-100)	1 (4.80)	0
Good (51-75)	10 (47.62)	2 (9.52)
Fair (26-50)	7 (33.33)	14 (66.67)
Poor (0-25)	3 (14.29)	5 (23.81)
Worsening	0	0

TABLE 2 Patient self-assessment for melasma improvement on HIFU-treated side and control side

induced hyper-pigmentation in skin type IV was observed when compared to controls, but not in skin type III participants.[5]

The present study was conducted in order to evaluate the efficacy and safety of HIFU in the treatment of melasma in Asians. The results revealed that HIFU-treated side attained greater reduction of mean RL*I after 3 sessions of treatment when compared to controls. Similar findings were observed in changes of mean $MASI_m$. After treatment, mean RL*I and mean mMASI significantly decreased from baseline in both sides. However, no statistically significant differences between two groups were detected. No patients suffered from worsening of melasma condition. In terms of patients' assessment, approximately half of the participants rated the improvement as more than 50% on HIFU-treated side, whereas the majority gave a 26%-50% improvement rating on the control side. The findings highlighted some positive effects of HIFU for the treatment of melasma. This can be supported by the proposed mechanism that HIFU induced vibration and friction, with consequent mechanical destructive effects which further eliminate melanin and pigmented debris from the epidermis and upper dermis.[4] Considering the previous report, HIFU seems to provide more favorable outcome in skin type IV than type III.[5] Nevertheless, skin type did not significantly affect the outcome of melasma either evaluated by RL*I or $MASI_m$ in this study. According to the study by Choi et al,[4] clinically favorable improvement in hyperpigmentation was observed as soon as 2-3 weeks after HIFU treatment. We thus hypothesize that 4-week-interval treatment could be relatively too long, and shorter treatment interval and/or higher number of HIFU sessions may yield more apparent effects.

In terms of side effects, pain was generally tolerable without local anesthesia. Only 1 patient reported burning sensation after HIFU treatment which was transient and subsided without treatment. Other side effects including scaling and erythema were considered to be related to hydroquinone, because they were not only present on HIFU-treated side but also on the control side. Interestingly, no worsening of melasma or post-inflammatory hyper-pigmentation was reported in our study. Given the fact that radiofrequency devices carry potential risk of PIH,[9,10] we propose that HIFU can be a better option for patients with skin laxity who have concurrent melasma.

The main limitation of the present study is small sample size that might have prevented us from detecting a statistically significant difference between the HIFU treatment and control. We also lacked participants with skin types other than type III and type IV. Thus, our findings may not be applicable to all skin types. Additionally, we might have suffered from some bias regarding patient's self-evaluation because the participants were not blinded to the treatment. Larger numbers of participants, a greater variety of skin types, double-blinding, and appropriate treatment intervals are therefore recommended for future studies on the clinical efficacy of HIFU in melasma. In addition, more studies of HIFU regarding treatment of various hyper-pigmented conditions beyond melasma should also be undertaken to indicate other potential indications.

In conclusion, HIFU may be an adjuvant in the treatment of melasma. However, both cost and effectiveness of HIFU should be taken into account. Further studies are warranted to indicate its efficacy.

Side effects	n = 21 (%)
Device-related side effects	
Burning sensation	1 (4.76)
Medication-related side effects	
Scaling	1 (4.76)
Erythema	1 (4.76)

TABLE 2 Side effect

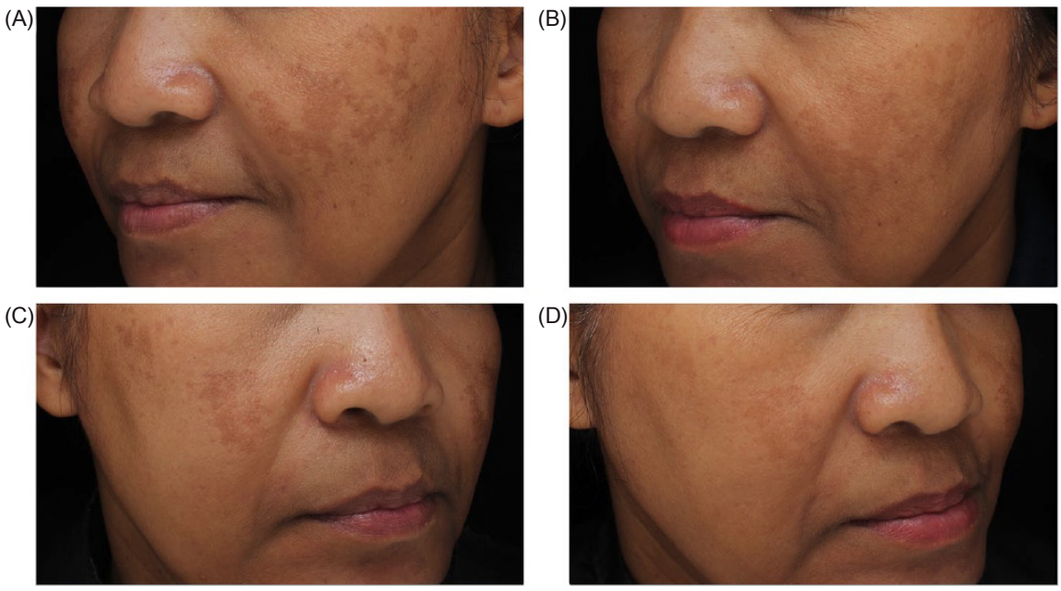

FIGURE 4 Photographs of patient with melasma. (A) Control side at baseline, (B) control side at 12th week, (C) HIFU-treated side at baseline, and (D) HIFU-treated side at 12th week

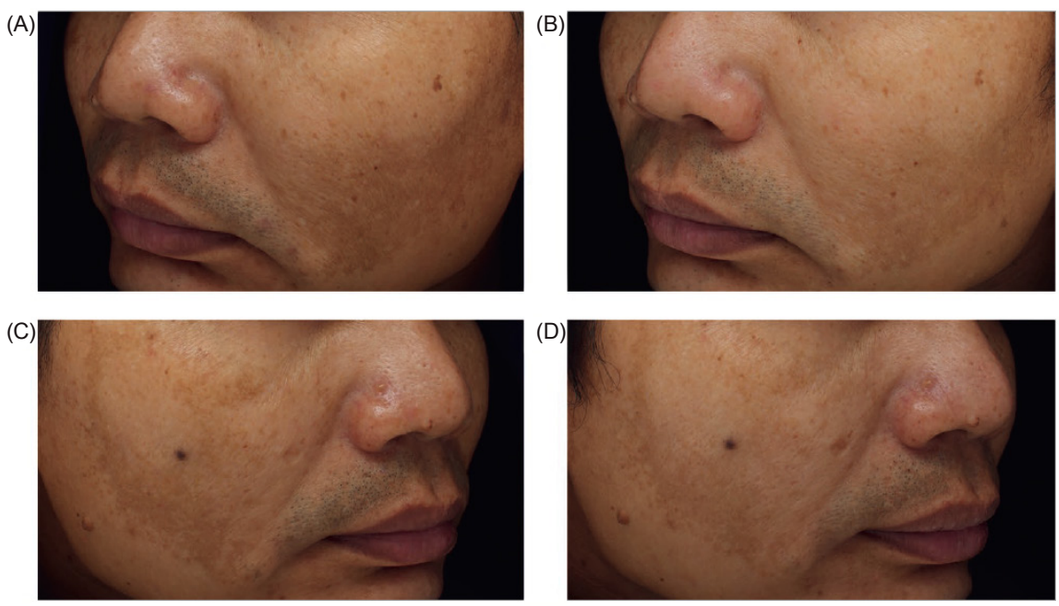

FIGURE 5 Photographs of patient with melasma. (A) HIFU-treated side at baseline, (B) HIFU-treated side at 12th week, (C) control side at baseline, and (D) control side at 12th week

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CONFLI CT OF INTEREST

The authors declare no conflict of interest.

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