

## Research Article

# The Safety and Efficacy of Macrofocused Ultrasound without Visualization on Enlarged Facial Pores among Thai Patients: A Pilot Study

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**Introduction.** Visibly enlarged facial pores are familiar dermatologic concerns. Macrofocused ultrasound energy without visualization (MaFU-WV) showed efficacy in facial tightening and an improvement in skin textural irregularities which opened the potential of the positive effects in reducing the appearance of facial pores. This study aims to assess the safety and efficacy of MaFU-WV in tightening facial pores. **Methods.** This was a prospective, single-blinded pilot study. Thirty-four Thai subjects with enlarged pores received a single treatment of MaFU-WV using a 2.0 mm transducer on bilateral malar areas of the face. Primary outcome measures included the pore count, pore volume, and pore index measurements using an instrument with a camera for image acquisition and software for analysis of skin. Secondary outcome measures incorporated two blinded dermatologists' evaluation of clinical photographs and the subjects' perception of improvement in their facial pores using a 6-point scale. Measurements were taken at baseline, 1 week, 1 month, 3 month, and 6 month after treatment. **Results.** The pore count significantly decreased from baseline to 6 month after treatment ( $p < 0.001$ ). Pore volume was significantly lowered from baseline to 1 week and 1, 3, and 6 months after treatment ( $p < 0.05$ ). The pore index was likewise significantly reduced from baseline in every visit ( $p < 0.05$ ). The majority of photographic evaluations by blinded dermatologists were scored as a 1–25% pore minimizing effect across nearly all follow-up visits. On the other hand, patient satisfaction kept improving until the end of the study at 6 months. No adverse events occurred throughout the conduct of the study. **Conclusion.** Macrofocused ultrasound energy using a 2 mm transducer is a safe and effective treatment for facial pore tightening. The trial is registered with registration number: TCTR20220719001.

## 1. Introduction

Facial pores by definition are enlarged openings of the pilosebaceous unit visible to the naked eye [1]. Several studies have sought to explore the factors that cause and contribute to enlarged facial pores in an attempt to direct treatment, but these yielded conflicting results [1–9]. The unifying conclusion is that the pathogenesis of enlarged facial pores is multifactorial and complex, thereby necessitating a similar approach in therapy [4]. The existing literature enumerates the pathomechanisms of enlarged pores

as consequences of increased sebum secretion that emphasize pore appearance, age-related decrease in collagen and elastin around pilosebaceous units, and thick hair follicles [2, 3]. Directing therapy toward these etiologies is therefore key to effective treatment. Albeit various therapeutics for this cosmetically bothersome condition have been considered, results remained to be challenging, not sustained, and modest at best.

Several treatment modalities have been explored in the literature. These range from topical and oral vitamin A derivatives, hormonal therapy, chemical peeling [1], intradermal

botulinum toxin injections [10, 11], light therapy such as intense pulsed light [12] and broadband light [13], and lasers including ablative [14], fractional ablative [15], and non-ablative lasers [16–19]. Other energy-based devices using acoustic waves [20] radiofrequency [21], fractional radiofrequency with micro-needling [22], and focused ultrasound technology with visualization, alone [23] or in combination with hyaluronic acid fillers have been used to reduce facial pores [24]. The unifying mechanism behind the efficacy of energy-based devices in minimizing the appearance of facial pores is a result of thermal-induced collagen and elastin remodeling around the follicular openings at the level of the dermis [14–24]. Although studies exist that explored the efficacy of microfocused ultrasound with visualization (MFU-V) on enlarged pores using 1.5 mm (10.0 MHz) and 3.0 mm depth (7.0 MHz) transducers [23, 24], no known clinical trial has been conducted using its macrofocused counterpart without visualization using a 2.0 mm transducer (5.5 MHz).

Related to this, a recent 2020 pilot study by Wanitphakdeedecha et al. [25] sought to determine the efficacy of this high-intensity macrofocused ultrasound device using the 2.0 mm transducer (5.5 MHz) for the treatment of upper facial laxity. Secondary parameters were measured in addition to the primary outcome of facial tightening and lifting. These included an improvement in skin textural irregularities, which incidentally included the finding of decreasing the appearance of facial pores. The positive findings from this research propelled the investigation of the current study. Hence, this pilot trial aimed to determine the safety and efficacy of a macrofocused ultrasound (MaFU) device using a 2.0 mm transducer (5.5 MHz) in tightening and reducing the appearance of facial pores.

## 2. Materials and Methods

**2.1. Study Design and Patient Selection.** This study utilized a prospective, single-center, evaluator-blinded pilot design conducted at a university hospital in Bangkok, Thailand. Thirty-four Thai subjects (7 men, 27 women; mean age  $35.38 \pm 5.88$ ; range 27–49; Fitzpatrick skin type III–V) with visibly enlarged facial pores perceived by the naked eye on the malar cheeks were recruited for the study. The exclusion criteria included pregnancy, pacemaker or implantation of any metallic device, history of facial surgery within 1 year from study treatment, history of thread-lifting using absorbable threads within 3 months, history of thread lifts using golden or metallic threads, history of botulinum toxin or soft-tissue augmentation injections within 2 weeks, neuropathy, history of keloid or a hypertrophic scar, active Herpes simplex infection, subjects with excessive subcutaneous fat or ptotic fat, and use of NSAIDs, aspirin, steroid, heparin, vitamin K, or vitamin E within 72 hours before treatment. Since the authors acknowledge that increased or excessive sebum secretion is a pathomechanism of enlarged facial pores, it was thereby necessary to exclude patients who have been on any form of treatment with vitamin A or its derivatives, specifically oral and topical forms of retinoids or its byproducts. In such cases where a subject was on any form of retinoid, a washout period of

1 month was required prior to enrollment in the study. This protocol was approved by the Institutional Review Board of the university. The patient's consent to participate in the trial was obtained after full explanation has been given of the treatment.

**2.2. Equipment Used.** This study utilized a macrofocused ultrasound (MFU) energy device (Ultraformer III (Shurink) Classys Inc., Seoul, Korea), with a 2.0 mm transducer to deliver the treatment. Microfocused cartridges have highly concentrated ultrasound beams that deliver power with accuracy and precision to the specified focal region. Macrofocused cartridges, on the other hand, operate with lower frequencies that allow deeper penetration to the focal region with a larger energy density.

The new macro 2.0 mm MF2 cartridge operating at 5.5 MHz frequency is a slimmer and faster transducer that offers no limitations on treatment regions. It is indicated for rhytids, lifting, improvement of texture, tone, and pore size.

**2.3. Photographic Setup and Digital Analyzers.** ANTERA 3D® CS (Miravex, Ireland) is a tool that contains a camera for image acquisition and software for analysis of skin. It measures an area of  $56 \times 56$  mm. The skin topography and the chromophore concentration are derived from analysis of the image data, obtained by illuminating the skin with LEDs of different wavelengths from different directions. The images acquired using ANTERA 3D® CS are independent of lighting conditions—achieved by a combination of polarizing filters and proprietary technology. This guarantees reproducible conditions and the accuracy of the results. Therefore, it can be used to evaluate skin color, wrinkle, texture, melanin, hemoglobin, pore, depression, and elevation [26].

**2.4. Treatment Preparation, Area Selection, and Settings.** All subjects received a single treatment of macrofocused ultrasound energy using a 2 mm (7.0 MHz) transducer on bilateral malar areas of the face. Topical anesthetic cream (5% EMLA®, AstraZeneca) was applied for 40 minutes prior to the procedure with occlusion. A thin layer of ultrasound gel was applied to the treatment site before the device was positioned perpendicular to the skin. Bilateral malar areas were treated using a 2.0 mm transducer with an energy pulse ranging from 0.3–0.4 J. A total of 60–130 shots were delivered to each cheek, individualized as per the size of the subject's face.

**2.5. Posttreatment Care.** After treatment, patients were instructed to apply a cold compress to the treated area to reduce pain and inflammation. They were advised on the use of broad-spectrum sunscreen, avoidance of extremes of temperature, and refraining from any cosmetic procedure throughout the duration of the study until 6 months follow-up.

**2.6. Photographic Analysis Process.** Primary outcomes were the measurements of the pore count, pore volume, and pore index at baseline; 1 week; and 1 month, 3 months, and

6 months posttreatment. Pore measurements were taken using ANTERA 3D® CS (Miravex, Ireland). Measurements were performed on the cheek area by placing the camera directly onto the skin without excessive pressure. Only pore-related parameters were analyzed in this study from triplicate measurements in the same area. This outlines the description of the pore parameters including the pore count, pore volume, and pore index measured from ANTERA 3D® CS: The pore count is defined as the number of individual pores detected [27]. Pore volume is the overall volume of skin indentations due to the presence of pores in the selected region, and the pore index is the overall score of skin porosity in the selected region of interest [27].

After subjects washed their faces with a mild, hypoallergenic, noncomedogenic cleanser, they sat in the waiting area at the university laser center for 10 to 15 minutes. Thereafter, all clinical photographs were taken using a digital camera (Canon PowerShot G9 stand-off camera (OMNIA Imaging System, Canfield Scientific Inc.)). Identical camera settings, lighting, and positioning were taken in the same room under identical environmental conditions. This process was replicated 5 times at baseline, 1 week, 1 month, 3 months, and 6 months posttreatment with the MFU device. The clinical photographs were assessed by two blinded dermatologists using a 6-point scale: 0 = worsening, 1 = no effect of minimization, 2 = 1–25% very mild pore-minimizing effect, 3 = 26–50% mild pore-minimizing effect, 4 = 51–75% moderate pore-minimizing effect, and 5 = 76–100% marked pore-minimizing effect. The ratings were compared between baseline and 1 week after treatment, 1 month after treatment, 3 months after treatment, and 6 months after treatment. The subjects were asked to quantify their perception of improvement in facial pores at each follow-up visit with the same scale as the blinded assessor. The pain score from the treatment was taken using a 10-point numerical rating scale, where 0 was no pain, and 10 was the worst imaginable pain felt. Adverse events, if any, were also documented.

**2.7. Statistical Treatment.** Descriptive analysis was used for the demographic data. All statistical analyses to compare baseline with posttreatment at 1 week, 1 month, 3 months, and 6 months for the pore count, pore volume, and pore index using ANTERA 3D® CS (Miravex, Ireland) were performed using statistical software (SPSS version 18.0; SPSS Inc., Chicago, USA), with a  $p$  value <0.05 indicating statistical significance. The Friedman test and the Wilcoxon test were utilized to determine significant differences from baseline across all follow-up visits for pore measurements obtained using ANTERA 3D® CS (Miravex, Ireland).

### 3. Results

Of all 34 patients enrolled in the study, 31 (91.2%) followed up for clinical photographs and pore parameter measurements using ANTERA 3D® CS by 1 week and 1-month follow-up; 30 (88.2%) came back by the 3<sup>rd</sup> month, while 20 (58.8%) subjects came for their final assessment at the

culmination of the study. However, those who were unable to come for their follow-up visits were telephoned to record their assessments of improvement through the 6-point scale described in the previous section. Since the study intervention was implemented only once, all patients received the treatment as per protocol. Albeit only 20 of the 34 subjects followed up for photographic assessment at 6 months, the sample size is still in excess of the recommended sample size for pilot trials [28]. This applies to pilot studies when there is no prior information to base a sample size on. For such studies, the recommendation is a sample size of 12 per group.

An example of clinical photographs, which the blinded dermatologists evaluated, is shown in Figure 1. The demographic data and the number of shots delivered per patient as well as the pain score are described in Table 1.

The subjective assessment of facial pores in the malar area via photographic evaluation by two blinded dermatologists using a 6-point grading scale is presented in Figure 2. In the first week posttreatment, most (39%) were assessed to have no pore-minimizing effect, while this improved by the first month where very mild pore minimization was noted in 35% of patients. The majority of patients were given a score of 2 or very mild pore minimization (1–25% pore-minimizing effect) across all follow-up visits, peaking at one-month follow-up, where 56% of patients were assessed to show very mild pore minimization from baseline. The proportion of patients given a higher score showed an increasing trend as they were followed up until 6 months. This is illustrated in Figure 2 as the percentage of patients given a score of 3, or 26–50% mild pore minimization, kept increasing from 1 week (21%), to 3 months (30%), and finally, through 6 months (38%) of follow-up. Only 2–5% of patients were ever given a score of 4 or moderate pore minimization throughout all follow-up visits, and none were given the highest score.

Giving a higher score than their assessors (39%) in the first week, only 15% of patients perceived their facial pores to be the same as baseline. Majority (38%) already noted very mild minimization on their pores one week after treatment. This further improved after one month, where the number of patients who perceived their pores to have mild or 26–50% minimization from baseline (score of 3) increased by 21% from the first week. By the 3<sup>rd</sup> month after treatment, none of the subjects gave a score that is lower than 3; all noted at least mild improvement in pore appearance. By the 6<sup>th</sup> month, the subjects' grade on pore tightening was banded mostly at score 2 or a very mild pore-minimizing effect. Of note, by the third and sixth months, 26% and 6% of subjects, respectively, started to note a 76–100% or marked improvement in the appearance of their pores, corresponding to the highest score of 5. Generally put, subjective pore-tightening effects were sustained, albeit to a lesser degree, by the end of the study at 6 months posttreatment, where 44% of patients rated their pore reduction effects as still very mildly minimized from baseline. The subject's perception of the degree of facial pore minimization from baseline is illustrated in Figure 3.

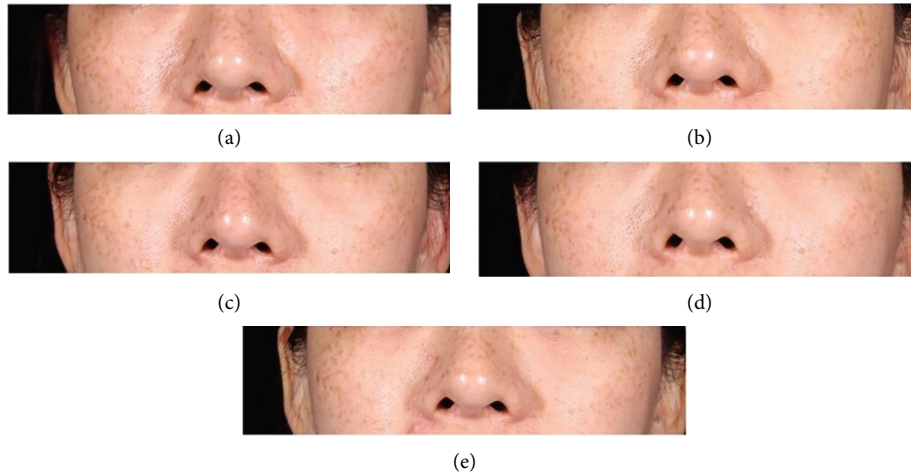


FIGURE 1: Clinical improvement of enlarged pores after 1 MaFU treatment from (a) baseline, (b) one-week follow-up, (c) one-month follow-up, (d) three-month follow-up, and (e) six-month follow-up.

TABLE 1: Demographic data of subjects enrolled in the study.

Characteristics	Value ( $n = 34$ )
Age in years	$35.38 \pm 5.88$
Mean $\pm$ SD* (min-max)	(27–49)
Sex, $n$ (%)	
Male	7 (20.59)
Female	27 (79.41)
Skin type, $n$ (%)	
III	1 (2.94)
IV	30 (88.24)
V	3 (8.82)
Number of shots per patient	
2.0 mm transducer	$183.12 \pm 29.19$
Mean $\pm$ SD* (min-max)	(120–260)
Mean pain score	$2.32 \pm 1.15$
Mean $\pm$ SD* (min-max)	(0–5)

\*SD, standard deviation.

For the three objective measurements of pore parameters using ANTERA 3D<sup>®</sup> CS, the pore count (Figure 4) significantly decreased from  $26.42 \pm 10.32$  at baseline to  $19.81 \pm 12.05$  at 6 months after treatment ( $p < 0.001$ ).

Pore volume (Figure 5) was significantly lowered in every visit, from  $0.55 \pm 0.50$  at baseline to  $0.46 \pm 0.49$  at 1 week,  $0.44 \pm 0.48$  at 1 month,  $0.42 \pm 0.57$  at 3 months, and  $0.36 \pm 0.57$  at 6 months after treatment ( $p < 0.05$ ). An example of ANTERA 3D digitally analyzed photographs for pore volume in one subject is shown in Figure 6.

The pore index (Figure 7) was likewise significantly reduced from baseline across all succeeding clinic visits, from  $4.73 \pm 3.20$  at baseline to  $3.92 \pm 3.29$  at 1 week,  $3.68 \pm 3.23$  at 1 month,  $3.38 \pm 3.40$  at 3 months, and  $2.48 \pm 2.29$  at 6 months after treatment ( $p < 0.05$ ).

The pain score from the treatment ranged from 0 to 5/10. One subject (3%) reported no pain. Seven subjects (21%) reported only very slight (score of 1/10) pain. Pain scores of 2, 3, and 5 were given by 35%, 32%, and 9% of patients, respectively. Other possible adverse events such as persistent

erythema, postinflammatory hypopigmentation or hyperpigmentation, bullous formation, crusting, oozing, burns, or scars were not observed in this study.

#### 4. Discussion

High-intensity macrofocused ultrasound (MaFU) without a visualization (Ultraformer III (Shurink) Classys Inc., Seoul, Korea) device using the 2.0 mm transducer that delivered ultrasound energy at 5.5 MHz transmission speed was safe and efficacious in the minimization of facial pores based on three parameters of pore characteristics, namely: pore counts, pore volume, and pore index, as measured using ANTERA 3D<sup>®</sup> CS (Miravex, Ireland). This may be explained by mechanisms that address two of the three pathophysiologies of enlarged facial pores. First, consistent with findings in another study using MFU-V [23], MaFU-induced thermal damage had a direct effect on the sebaceous glands at the level of the dermis results in mitigating excessive sebum secretion. Second, the deliverance of high-intensity, accurate beams of ultrasonic waves induces molecular vibrations, leading to the generation of thermal energy at approximately  $65.4^{\circ}\text{C}$  in focal zones of coagulation at the deeper tissue plane, which stimulates dermal neocollagenesis and elastogenesis to strengthen perifollicular structural support [23, 24, 29]. In addition to bolstering perifollicular support, Prieto et al. [30] found that photothermal tissue interactions induced dermal dendritic cells to express protein HSP-70 and procollagen 1. It was postulated that these cells participate in the deposition of dermal collagen in the opening of enlarged hair follicles, which collectively contribute to the reduction of sizes of pores.

To differentiate the two, MFU-V utilized the 3.0 mm and 1.5 mm transducers that delivered microfocused beams with a thermal coagulation point of 0.5 mm in diameter in the dermis [25, 29]. In contrast, the 2.0 mm transducer delivered macrofocused beams that coagulated a larger area (1.0 mm) to stimulate collagen remodeling effectively [25].

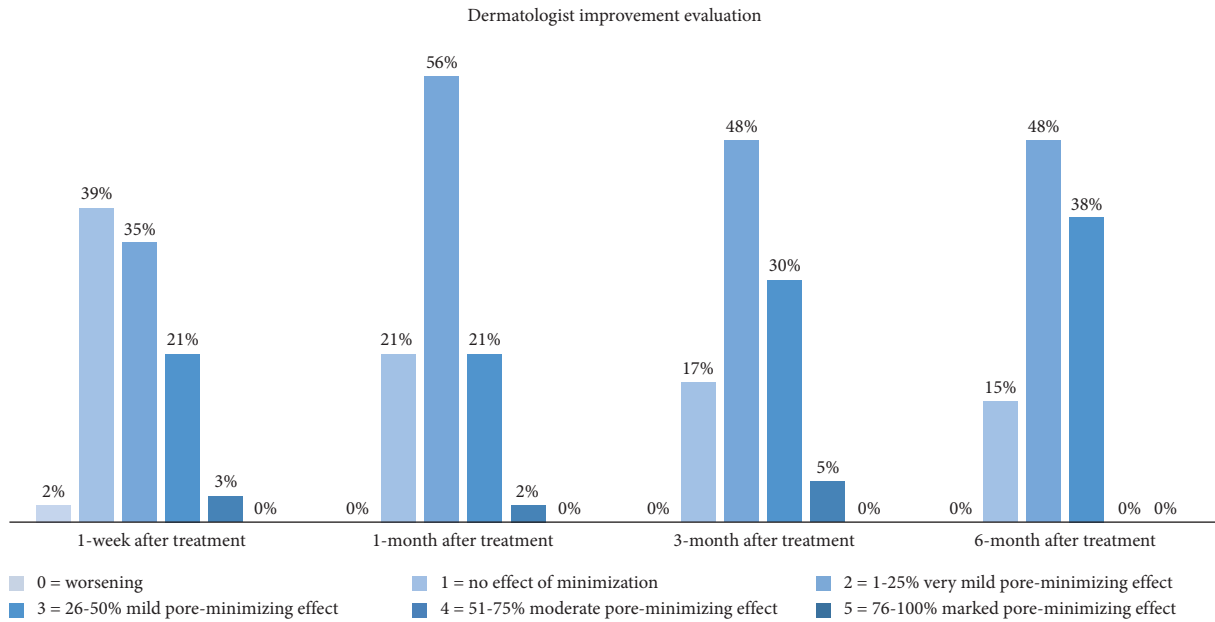


FIGURE 2: Scoring of the degree of pore minimization by photographic evaluation by two blinded dermatologists.

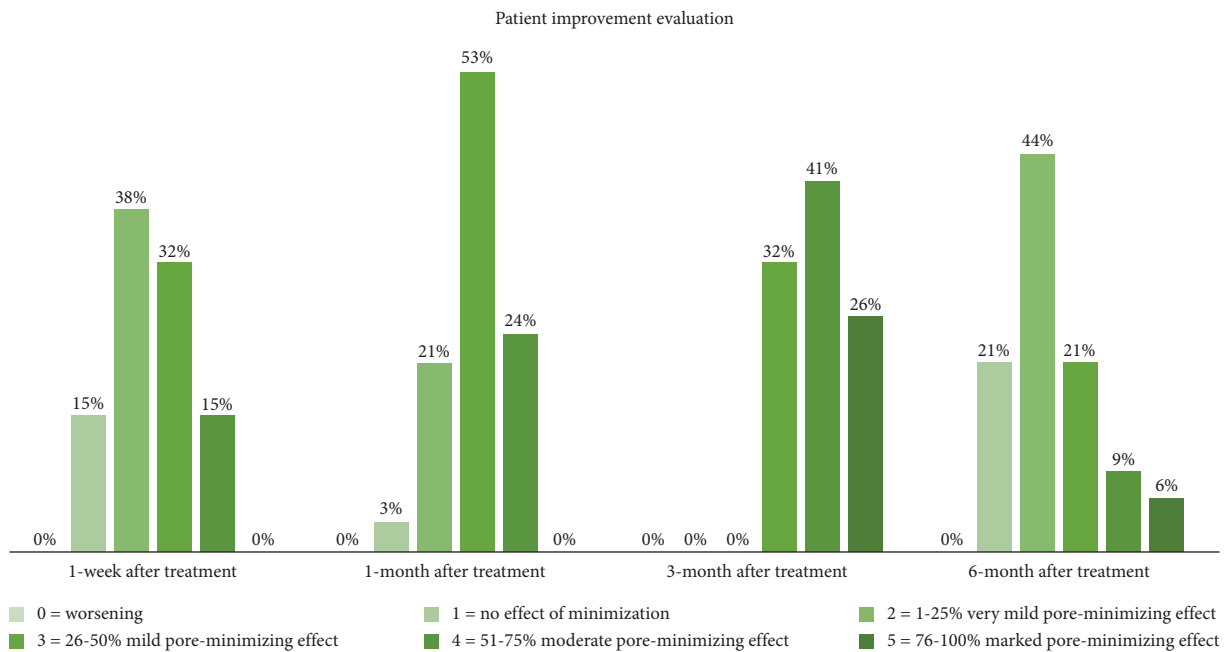


FIGURE 3: Patient's perception of the degree of pore minimization from baseline.

Although pore counts showed a decreasing trend, values were only statistically significant by the six-month follow-up. This may be because thermal injury-induced dermal reassembly may occur for up to six months of treatment [23].

Participants in the study reported pain from the procedure as none (0/10) to moderate at most (5/10). There was also no occurrence of erythema, itching, edema, formation of crusts or scabs, hypopigmentation, hyperpigmentation, acneiform eruption, and pain [2, 3, 14–19, 21, 22, 30]. With

high-intensity, macrofocused technology, uniform ultrasound energy is directed into target layers of skin without heat diffusion to surrounding tissue, thereby sparing unintended areas or layers of tissue during treatment. With the 2.0 mm transducer, the epidermis and tissue deep to the reticular dermis are spared. This can account for the minimal pain felt and the absence of other side effects while delivering equally effective to superior results in just one session, which, in this study, remained sustained up to six months.

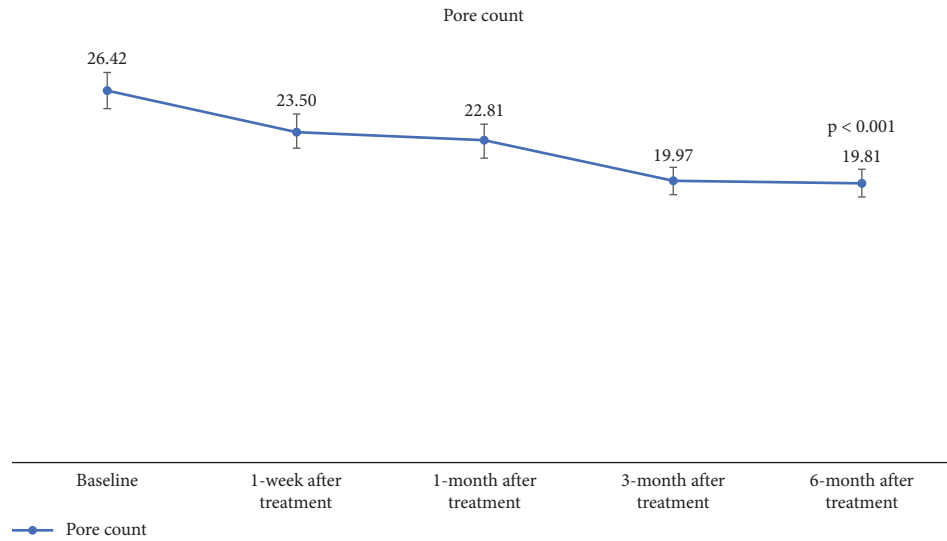


FIGURE 4: Pore count measurements by ANTERA 3D®.

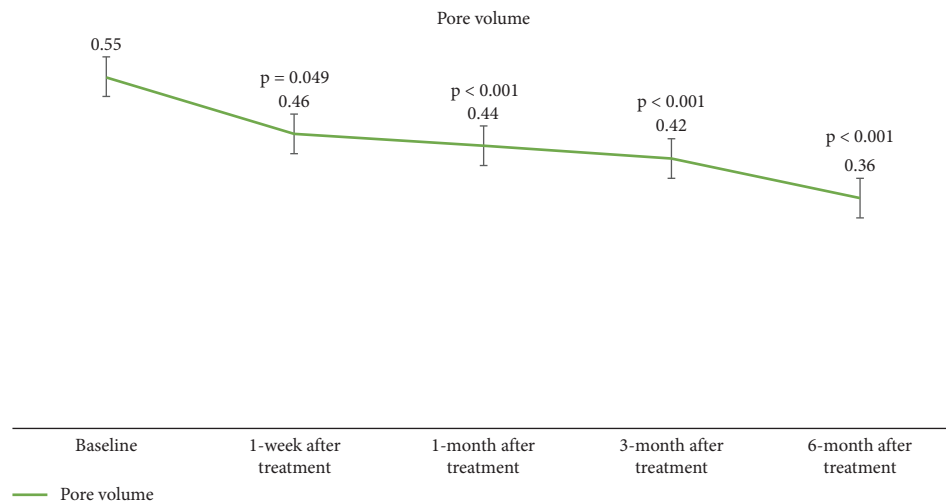


FIGURE 5: Pore volume measurements by ANTERA 3D®.

Subjective evaluation by blinded dermatologists and the subjects showed an improvement in the appearance of pores. The majority of subjects gave higher scores than their assessors in the first week through the sixth month of follow-up visits. Although the percentage of patients who perceived a marked improvement in their pores decreased to 6% by the end of the study from 26% from the 3<sup>rd</sup> month, it is significant to point out that in no instance during the study did the blinded evaluators give the same highest possible score to any patient. These discrepancies between patient and assessor ratings are indicators of patient satisfaction. With only a single session in the absence of scrupulous pre-procedure preparation, visible results were evident as early as one week after treatment that were sustained—even improved for some—until the end of the study at 6 months without further treatment. Furthermore, subjects were relatively comfortable during the procedure, experienced no downtime, and encountered no adverse events. Although

inherent mechanisms of effectiveness are similar to its MFU analog, studies on the latter reported treatment-related events such as the incidence of transient erythema and/or edema, feelings of tightness up to 2 weeks with the 3.0 mm transducer, edematous striations with the 1.5 mm transducer [23], erythematous welts, and bruising [24]—none of which occurred with the 2.0 mm transducer MaFU device used in this study.

Also, offering the advantage of sparing the epidermis from injury, Roh et al.'s study [17] significantly tightened pores and decreased sebum production by the use of various parameters of long-pulsed 1064 nm Nd: YAG laser. Five sessions of treatment spaced 3 weeks apart were performed to yield clinical endpoints comparable to this study. However, complications such as folliculitis and aggravation of pre-existing melisma were reported. A downtime of 7 days was also noted. Nevertheless, pore-tightening effects were noted until its completion 2 months after the last session.

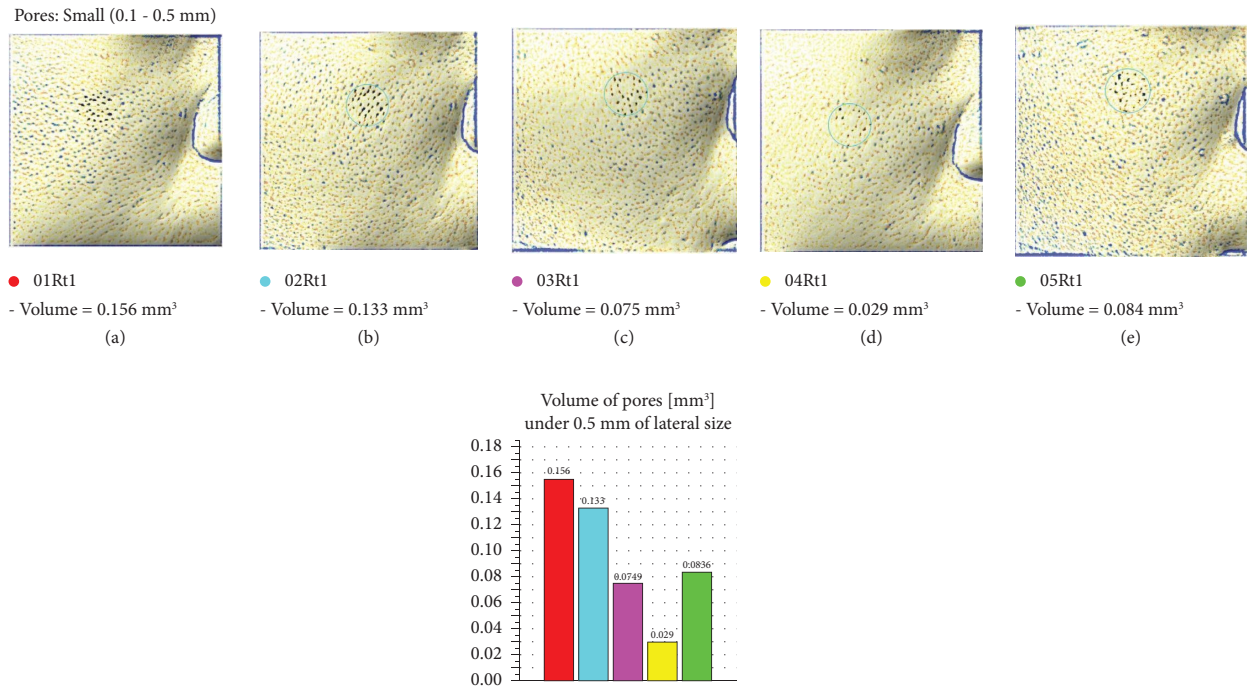


FIGURE 6: ANTERA 3D digitized analyzed photographs for pore volume in one subject after 1 MaFU treatment from (a) baseline, (b) one-week follow-up, (c) one-month follow-up, (d) three-month follow-up, and (e) six-month follow-up.

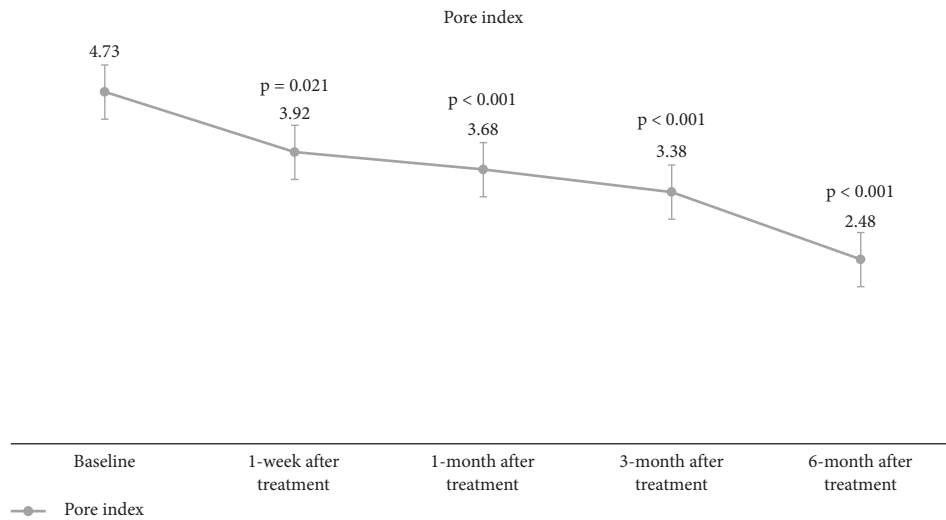


FIGURE 7: Pore index measurements by ANTERA 3D®.

These desired effects were equally achieved in the current study with only 1 session of MaFU and without unwanted adverse events. Even better, the result of pore tightening showed an improving trend that was statistically significant until 6 months.

In another study by Cho et al. [22], the effect of fractional bipolar radiofrequency microneedle (FRM) treatment in the reduction of large pores and acne scars was explored. Two sessions performed 4 weeks apart showed efficacy in both pore minimization and acne scar by the last follow-up at

12 weeks. However, there was no improvement in 23%, and the worsening of pores was quantified in one subject. Furthermore, exacerbations of skin texture and density were noted until 8 weeks. Some patients complained of intractable pain during the procedure, which persisted for a few days. Our study yielded superior results in objective pore measurements shown in the constant increasing trend in an improvement in pore parameters across all follow-ups, without noted adverse events and sustained improvement for a longer period.

**4.1. Limitations and Recommendations.** One limitation of this study is the incidence of dropouts, particularly by 6 months, where the last set of data hampered the statistical power of this research. It may be recommended to take the time to arrange clinic visits with the subjects early on, to schedule reminders at frequent intervals, or to offer incentives at the completion of the study. Second, albeit this study hypothesized MaFU to have a destructive effect on the sebaceous glands that contribute to the less pronounced appearance of pores, sebum production was not objectively measured. In a study by Lee et al. on the effect of MFU on enlarged facial pores in Asian skin [23], sebum production was decreased, yet not deemed statistically significant. This is in contrast with Roh et al. [17]. The abovementioned studies measured sebum levels objectively; therefore, it is recommended to include a measurement for sebum parameters, if further studies on the MaFU are to be explored. Third, MaFU may not address the last pathophysiology of enlarged pores, which is the thick density of the hair follicles on the face. Hence, it may be prudent to investigate combining MaFU with hair reduction or epilation procedures, and whether or not these performed alone or in combination would yield significantly different results. Lastly, being inherently cosmetic concerns, patients who seek treatment for enlarged facial pores are assumed to be long-term clients. In this study, as results were sustained until 6 months, it would be interesting to follow the subjects for a longer period of time to ascertain precisely when effects start to decline, and thereby, retreatment is necessary for sustained results and patient satisfaction. This will direct patient consultations and influence expectations, and ultimately, compliance with the treatment plan.

## 5. Conclusion

High-intensity macrofocused ultrasound treatment with a 2.0 mm transducer is safe and effective for pore tightening. This study showed a consistent improvement in the appearance of facial pores until 6 months. Hence, in treatment planning, additional MaFU treatments may be considered not earlier than 6 months after the first session. Compared to other modalities, unique to the MaFU technology in the treatment of enlarged facial pores is its advantage of offering accuracy and efficiency in target layer treatment with minimal to no downtime. Clinical results were achieved in just one session, which, in this study, was sustained for up to 6 months, and possibly longer.

## Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

## Additional Points

*Key Summary Point.* (i) Why carry out this study? (1) Macrofocused ultrasound energy without visualization showed efficacy in facial tightening and an improvement in

skin textural irregularities which opened the potential of the positive effects in reducing the appearance of facial pores. (2) This study aims to assess the safety and efficacy of macro-focused ultrasound energy without a visualization device in tightening facial pores in Asians. (ii) What was learned from the study? (1) Macrofocused ultrasound energy significantly reduced the pore count, pore volume, and pore index up to 6-month follow-up visits with a very mild improvement in facial pores graded by dermatologists and patient satisfaction across all follow-up visits. (2) Macrofocused ultrasound energy using a 2mm transducer is a safe and effective treatment for facial pore tightening.

## Ethical Approval

The study was approved by the Ethics Committee of the Siriraj Institutional Review Board (si 609/2017). This study was performed in accordance with the Helsinki Declaration of 1964 and its subsequent amendments.

## Consent

Written informed consent was obtained for the publication and use of all patients' images prior to their enrollment in the study.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

## Authors' Contributions

All the authors contributed to the study's conception and design. Chadakan Yan, Noldtawat Viriyaskultorn, Thanyaporn Leesanguankul, Thrit Hutachoke, Ya-Nin Nokdhes, Panittra Suphatsathienkul, and Rungsima Wanitphakdeedecha performed material preparation, data collection, and analysis. Rungsima Wanitphakdeedecha had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. The first draft of the manuscript was written by Katrina Kashmyr Borjal Kua-Uy, and all the authors commented on previous versions of the manuscript. All the authors have read and approved the final manuscript. All named authors meet the International Committee of Medical Journal Editors criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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