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# Contents

# Safety and efficacy of high-intensity focused ultrasound for treatment of periorbital, perioral, and neck wrinkles: Prospective open single-center single-arm confirmatory clinical trial

Hye Sung Han I Jae Wan Park I Soo Yeon Kim I Kwang Ho Yoo
Sun Young Choi I Beom Joon Kim

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Safety and efficacy of high-intensity focused ultrasound for treatment of periorbital, perioral, and neck wrinkles: Prospective open single-center single-arm confirmatory clinical trial

Hye Sung Han[1] I Jae Wan Park[1] I Soo Yeon Kim[2] I Kwang Ho Yoo[3] I Sun Young Choi[1] I Beom Joon Kim[1] I South Korea

[1]Department of Dermatology, College of Medicine, Chung-Ang University Hospital, Seoul, South Korea
[2]CLASSYS Inc., Seoul, South Korea
[3]Department of Dermatology, Chung-Ang University Gwangmyeong Hospital, Chung-Ang University College of Medicine, Gwangmyeong-si, South Korea

**Correspondence**
Beom Joon Kim, Department of Dermatology, Chung-Ang University College of Medicine, 102, Heukseok-ro, Dongjak-gu, Seoul 06973, South Korea.
Email: beomjoon74@gmail.com

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CLASSYS Inc.

**Abstract:** Periorbital, perioral, and neck wrinkles are one of the most common concerns of aging skin. We evaluated the efficacy and safety of high-intensity focused ultrasound (HIFU) device with a 5.5-MHz transducer and a 2.0-mm focal depth for improving periorbital, perioral, and neck wrinkles. A total of 102 participants were enrolled, and 34 each were assigned to the periorbital, perioral, and neck groups. All subjects were treated with HIFU three times at 2-week intervals at the corresponding treatment site. Objective measurements and clinical evaluations were performed at 10 and 16 weeks after treatment. Based on the primary efficacy evaluation, the mean Cutometer R7 value was significantly increased at 10 weeks post-treatment compared to baseline in all treated groups. In addition, all other Cutometer values, PRIMOS and Antera 3D camera evaluation results, classification of wrinkle assessment results, and Subject Global Aesthetic Improvement Scale also showed that the periorbital, perioral, and neck wrinkles were significantly improved at 10 and 16 weeks post-treatment.
No permanent adverse effects were observed during the follow-up period. HIFU treatment using 5.5-MHz transducers (2.0-mm focal depth) could be an effective and safe treatment modality for the treatment of periorbital, perioral, and neck wrinkles.

**Keywords:** high-intensity focused ultrasound, tightening, wrinkles

## 1 INTRODUCTION

Wrinkles are the most prominent features of the aging skin, and are most noticeable in the periorbital, perioral, and neck areas. To solve this problem, there is an increasing demand for safer and effective non-invasive treatments with low risk and minimal downtime. Intensity-focused ultrasound (IFU), including micro-focused ultrasound with visualization (MFU-V) and high-intensity focused ultrasound (HIFU), has recently been used widely for skin tightening and rejuvenation because it non-invasively delivers focused ultrasound energy, creating microcoagulation zones and result in gradual neocollagenesis and improved tissue elasticity.1–4 This clinical study aimed to evaluate the efficacy and safety of a HIFU device with a 5.5-MHz transducer and a 2.0-mm focal depth for improving periorbital, perioral, and neck wrinkles using measurable and objective results.

## 2 MATERIALS AND METHODS

### 2.1 | Ethics approval

This 16-week prospective single-center single-arm clinical study was conducted at Chung-Ang University Hospital in Seoul, Korea. The study was approved by the hospital's institutional review board (IRB no. 1931-004-365). Informed consent was obtained from all patients.

### 2.2 | Subject selection

Male and female patients aged 30–65 years with classification of wrinkles assessment scores (Table S1) of 1–5 in the periorbital, perioral, and neck areas were recruited. Informed consent was obtained from all participants. Exclusion criteria were a history of laser treatment, botulinum toxin, or filler injection in the past 6 months, deep chemical peeling or liposuction in the past 12 months, use of topical steroids or retinoids in the past 4 weeks, or an active skin infection or inflamed open wounds and scarring over the treatment area. A total of 102 participants were enrolled in this clinical trial; of them, 34 each were assigned to the periorbital, perioral, and neck groups.

### 2.3 | HIFU device and treatment procedures

The HIFU device used was the SHURINK (ULTRAFORMER III) (CLASSYS INC., Seoul, Korea). We used transducers, which deliver 0.1–0.4 J of energy at a fixed focal depth of 2.0 mm with frequency of 5.5 MHz. Treatments were performed three times at 2-week intervals (weeks 0, 2, and 4) (Table 1). Topical anesthetic EMLA cream (AstraZeneca, Sweden) was applied for 45–60 min before the treatment. For each group, the treatment area was 10.5 25.5 mm2, and a total of five shots (lines) were applied to the treatment area at 2.5-mm intervals. Ten treatment areas were used in the periorbital and perioral groups versus 16 in the neck group (Figure 1). Treatment applied to each 10 or 16 areas were defined as one pass and four passes were applied. The energy set during the procedure was 0.2–0.3 J (Table S2).

### 2.4 | Efficacy assessments

We used Cutometer®, 3D skin measurement systems including PRIMOS lite (Phaseshift Rapid In-vivo Measurement Of Skin, GFMesstechnik GmbH, Germany) and Antera 3D camera (Miravex, Ireland), classification of wrinkle assessments, and Subject Global Aesthetic Improvement Scale (SGAIS) (Table 2). The primary endpoint was changes in Cutometer R7 values measured at 10 weeks compared to baseline (0 week) (mean difference). The secondary endpoints were changes in other Cutometer values (R2 and R5) measured at 10 weeks compared to baseline (0 week), changes in R7 values measured at 16 weeks compared to baseline (0 week), values measured by PRIMOS lite (periorbital group), and Antera 3D camera (perioral and neck groups), changes in classification of wrinkles assessment and SGAIS (Table 1).

### 2.5 | Pain and safety evaluations

Immediately after each treatment and on weeks 6, 10, and 16 after the application of HIFU, subjects rated their pain after the application according to the numerical rating scale (NRS) consisting of 11 levels (0–10 points). All adverse events (AEs) occurring during this clinical trial were included in the safety evaluation. Vital signs were measured at each visit, and laboratory tests and physical examinations were performed at baseline and at the end of the study.

| Visit | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| Period | Screening | 1st treatment | 2nd treatment | 3rd treatment | 1st follow up | 2nd follow up | 3rd follow up |
| Time | 1 week | 0 week ± 7 days | 2 weeks ± 7 days | 4 weeks ± 7 days | 6 weeks ± 7 days | 10 weeks ± 7 days | 16 week ± 7 days |
| Primary endpoint | | | | | | Changes in Cutometer R7 values measured at 10 weeks compared to baseline | |
| Secondary endpoints | | | | | | Changes in Cutometer R2, R5 values measured at 10 weeks compared to baseline | Changes in Cutometer R7 values measured at 16 weeks compared to baseline |

**Table-1** Treatment sessions and endpoints





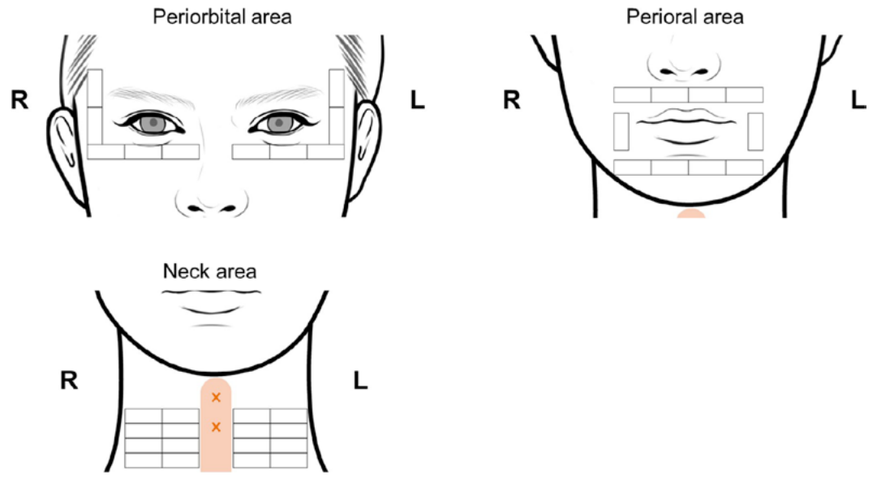


**Figure 1** Treatment maps of the periorbital, perioral, and neck areas

| R parameters of Cutometer® | |
|---|---|
| R2 | Gross elasticity, overall elasticity of the skin, including crepe recovery |
| R5 | Net elasticity |
| R7 | Biological elasticity, ratio of elastic recovery to total deformation |
| **Parameters of Primos lite** | |
| Ra | Average skin roughness |
| Rz | Average maximum skin roughness |
| **Wrinkle parameters of Antera 3D** | |
| Overall size | Average cross-section of the selected wrinkle |
| Depth | Average depth of the selected wrinkle |
| Maximum depth | Maximum depth of the selected wrinkle |
| **Global Aesthetic Improvement Scale (SGAIS)** | |
| **Grade** | **Evaluation criteria** |
| 4 | Marked improvement (76%–100%) |
| 3 | Moderate improvement (51%–75%) |
| 2 | Mild improvement (26%–50%) |
| 1 | Minimal improvement (1%–25%) |

**Table-2** Explanations of efficacy assessments

### 2.6 | Statistical analysis and data presentation

The statistical analyses were performed using SPSS version 25.0 for Windows (SPSS Inc., Chicago, IL, USA) and R program (version 4.0.3). The main analysis group was the FAS, and an additional analysis was conducted with the PPS (per-protocol set). We used the Hochberg step-up method to adjust the values for multiple comparisons. For the primary endpoint, we adjusted the one-sided 97.5% confidence interval to test the hypothesis; for the secondary endpoint, we adjusted the two-sided 5% significance level to test the hypothesis. A paired Student's t-test or Wilcoxon signed-rank test was used to compare efficacy.

## 3 | RESULTS

### 3.1 | Patient distribution and baseline characteristics

A total of 103 participants were recruited, 102 were enrolled, and 99 participants (97.06%) completed the clinical trial. The participants' baseline demographic characteristics in each group are shown in Table S3. The mean total energy applied to the participants in each group is shown in Table 3.

### 3.2 | Primary outcome: Comparison of Cutometer

R7 values at week 10 versus baseline Based on the FAS analysis, the mean Cutometer R7 value in the periorbital group was 0.287 ± 0.118 at baseline versus 0.378 ± 0.134 after 10 weeks. In the perioral group, the mean Cutometer R7 value was 0.276 ± 0.068 at baseline versus 0.391 ± 0.077 after 10 weeks. In the neck group, the mean Cutometer R7 value was 0.333 ± 0.145 at baseline versus 0.534 ± 0.092 after 10 weeks (Figure 2A).

| Treatment | | | | N (%) |
|---|---|---|---|---|
| Treatment per protocol—three times | | | | 100 (98.04) |
| | Energy (J) | Number of 1.05 x 2.55 $cm^2$ squares | Number of shots (mm length)/square (shot) | Total energy (J) |
| Periorbital group | | | | |
| 1st treatment Mean ± SD | 0.29 ± 0.02 | 10 ± 0 | 200 ± 0 | 1000 ± 81.20 |
| 2nd treatment Mean ± SD | 0.29 ± 0.03 | 10 ± 0 | 200 ± 0 | 980 ± 111.19 |
| 3rd treatment Mean ± SD | 0.29 ± 0.03 | 10 ± 0 | 200 ± 0 | 990 ± 97.89 |
| Perioral group | | | | |
| 1st treatment Mean ± SD | 0.25 ± 0.05 | 10 ± 0 | 200 ± 0 | 834.80 ± 169.30 |
| 2nd treatment Mean ± SD | 0.28 ± 0.04 | 10 ± 0 | 200 ± 0 | 968.48 ± 123.80 |
| 3rd treatment Mean ± SD | 0.29 ± 0.02 | 10 ± 0 | 200 ± 0 | 999.39 ± 82.38 |
| Neck group | | | | |
| 1st treatment Mean ± SD | 0.25 ± 0.05 | 16 ± 0 | 319.41 ± 3.43 | 1337.55 ± 270.98 |
| 2nd treatment Mean ± SD | 0.27 ± 0.05 | 16 ± 0 | 320 ± 0 | 1453.96 ± 248.35 |
| 3rd treatment Mean ± SD | 0.28 ± 0.04 | 16 ± 0 | 320 ± 0 | 1517.12 ± 214.99 |

**Table-3** Treatment results

The mean Cutometer R7 was significantly increased at 10 weeks post-treatment versus baseline in all treated groups. The greatest increase was observed in the neck group.

## 3.3 | Secondary outcomes

### 3.3.1 | Changes in R2, R5, and R7 values according to the Cutometer

The mean Cutometer R2 value was significantly increased at 10 and 16 weeks post-treatment compared to baseline in all treated groups (Figure 2B). Similarly, the mean Cutometer R5 value was significantly increased at 10 and 16 weeks post-treatment versus baseline in all treated groups (Figure 2C). Finally, the mean Cutometer R7 value was significantly increased at 16 weeks post-treatment versus baseline in all treated groups (Figure 2A).

### 3.3.2 | Changes in values measured by PRIMOS lite and Antera 3D camera

The mean Ra and Rz values according to PRIMOS lite were significantly decreased at weeks 10 and 16 post-treatment versus baseline in the periorbital group (Figure 2D,E). The mean overall size, mean depth, and maximum depth values according to the Antera 3D camera were significantly decreased at weeks 10 and 16 post-treatment versus baseline in the perioral and neck groups (Figure 2F-H).

### 3.3.3 | Classification of wrinkle assessment and SGAIS results

Evaluation of the mean classification of wrinkle assessment scores revealed an overall decrease in all treatment groups (Figure 3). In the periorbital group, the mean score started to decrease significantly in week 4 (after the second treatment) and further decreased during week 6 (after the third treatment), and this mean score was maintained until 16 weeks post-treatment. In the perioral and neck groups, the mean score started to decrease significantly at week 10 after treatment and further decreased after 16 weeks.

In all three groups, the mean SGAIS score was greater than 1 at 4 weeks post-treatment and continued to increase over time (Figure 4A). In the periorbital group, all participants (100%) reported more than minimal improvement at week 10 and more than mild improvement at week 16. In the perioral group, 30 (93.75%) and all





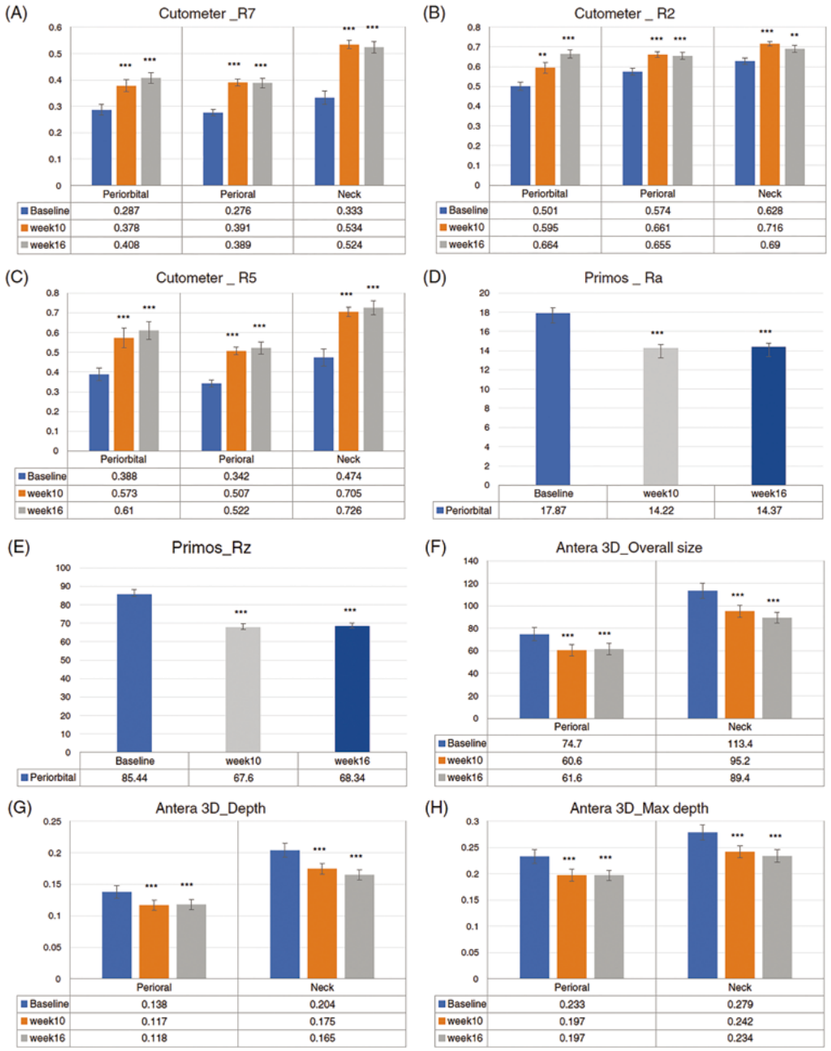


**Figure 2** Primary and secondary outcomes. ***p <0.001. (A) Changes in Cutometer R7 values measured at 10 and 16 weeks versus baseline. (B) Changes in Cutometer R2 values measured at 10 and 16 weeks versus baseline. (C) Changes in Cutometer R5 values measured at 10 and 16 weeks versus baseline. (D, E) Changes in values measured by the PRIMOS lite (periorbital group) at 10 and 16 weeks versus baseline. (F–H) Changes in values measured by the Antera 3D camera (perioral and neck groups) measured at 10 and 16 weeks versus baseline

participants (100%) reported minimal to marked improvement at week 10 and at week 16, respectively. In the neck group, 29 (87.88%) and 30 (90.91%) participants reported minimal to marked improvement at week 10 and at week 16, respectively (Figure 4B).

## 3.4 | Pain NRS evaluation

The mean pain NRS score were 0.76 ± 0.99 and 1.03 ± 1.40 immediately after the first treatment in the periorbital and perioral group,

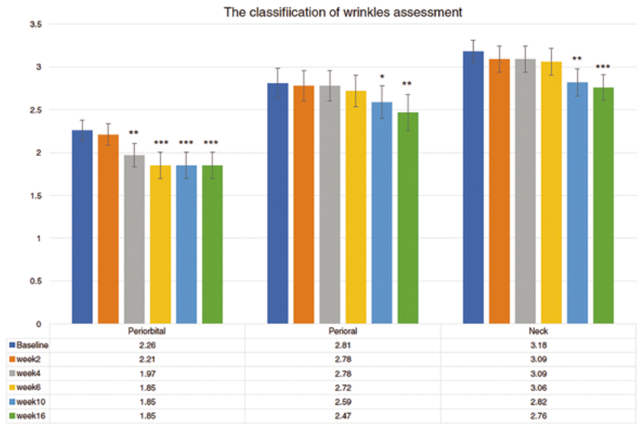


**Figure 3** Changes in mean score by classification of wrinkle assessment. *p <0.05, **p <0.01, ***p <0.001

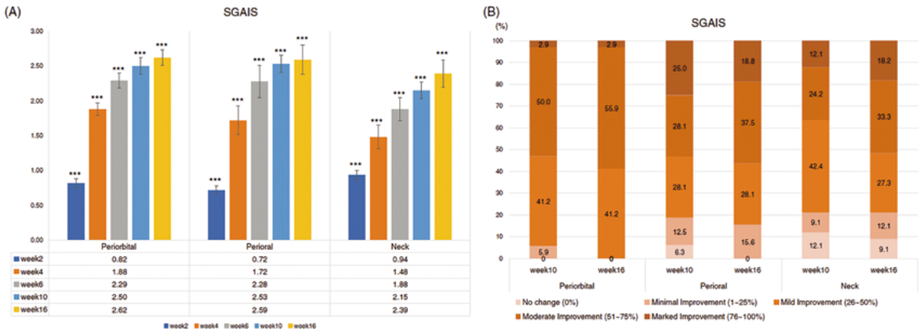


**Figure 4** Changes in mean Subject Global Aesthetic Improvement Scale (SGAIS) score. ***p <0.001

respectively, and decreased as the procedure was repeated (Figure 5). In the neck group, the mean NRS score was greatest at 2.47 ± 1.85, but it decreased over time. One participant complained of residual pain (NRS 1) before the second and third treatments, and at 6, 10, and 16 weeks after the completion of treatment. However, the pain completely disappeared at the fourth unscheduled visit.

### 3.5 | Safety

The physical examination results remained stable during the study period. Among the 102 subjects, 87 (85.29%) developed AEs (Table S4). AEs included application site pain (76 cases), application site erythema (65 cases), application site oedema (31 cases), application site pruritus (3 cases), and medical device site burning sensation (1 case). All pain and AEs that occurred after the procedure disappeared. There were no cases of linear striations, hypopigmentation, hyperpigmentation, ulceration, or erosion. There were also no severe AEs such as nerve or muscle dysfunction, severe pain, bruising, or bleeding.

### 3.6 | Correlation analysis of values measured with Cutometer® and PRIMOS

There was a significant negative correlation between the Cutometer R2 value (gross elasticity) and the PRIMOS Ra value (average roughness of skin) (Pearson's correlation = 0.437, p = 0.010). There was also a significant negative correlation between the Cutometer R7 value and PRIMOS Ra value (Pearson's correlation = 0.341, p = 0.048). These findings indicate that the periorbital wrinkles improved as the skin elasticity improved.





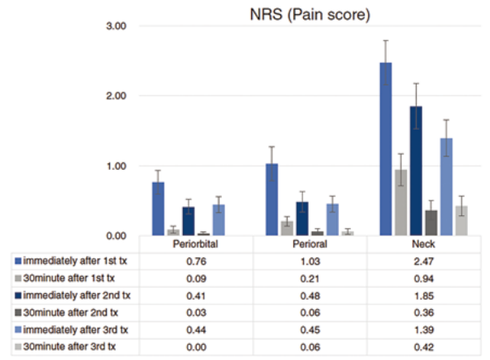


**Figure 5** Mean numerical rating scale pain score measured immediately and 30 min after each treatment

### 3.7 | Comparison by age group and Fitzpatrick skin type

We compared the clinical outcomes by age group and Fitzpatrick skin type. After 10 weeks of treatment, the mean improvement in the Cutometer R7 value was significantly greater in the younger age group (<51 years) than in the older age group (≥51 years) (p = 0.013). The improvement in mean clinical wrinkle assessment scores was also greater in the younger age group than in the older age group, but the difference was not statistically significant. There was no significant difference in clinical outcomes by Fitzpatrick skin type.

## 4 | DISCUSSION

In this study, we used objective modalities including Cutometer®, PRIMOS, and Antera 3D camera to evaluate skin elasticity and wrinkle improvement after HIFU treatment because although physician- or patient-based assessments are important, they are often limited by inherent subjectivity (Figure S1). For the primary efficacy evaluation, we evaluated the Cutometer R7 value because it represents biological elasticity and is among the most common parameters used to assess skin aging or the efficacy of rejuvenation treatments.[5–7] The Cutometer® measures elasticity of the upper skin layer using negative pressure which deforms the skin mechanically. The primary efficacy evaluation confirmed that the skin elasticity of the periorbital, perioral, and neck areas significantly increased 10 weeks after treatment versus baseline. Furthermore, the Cutometer R7 value continued to increase until 16 weeks in the periorbital area. The mean baseline Cutometer R7 value was the highest in the neck group, which is consistent with previous studies showing that the neck skin is more extensible with higher R values than those of the other sites.[8,9]

In addition, all secondary efficacy evaluation results, including the Cutometer R2, R5, and R7 values, PRIMOS evaluation (periorbital wrinkles), and Antera evaluation (perioral and neck wrinkles), classification of wrinkle assessment results, and SGAIS, showed that the periorbital, perioral, and neck wrinkles were significantly improved at 10 and 16 weeks post-treatment. We used different 3D imaging systems for the periorbital versus perioral and neck areas because the PRIMOS is most widely used to quantify periorbital wrinkles,[10,11] whereas Antera 3D cameras are mostly used to quantify wrinkles of the lower face.[12,13] The results revealed that wrinkles in all three treatment areas were significantly improved after HIFU treatment. Furthermore, the changes in Cutometer R7 value correlated well with the PRIMOS Ra value (Pearson's correlation = 0.437, p = 0.010), indicating that improvements in skin elasticity were highly correlated with improvements in wrinkles.

Regarding treatment efficacy, although no studies have evaluated the improvement of wrinkles using all of the objective measurements used in this study, numerous studies evaluated IFU devices in facial skin rejuvenation using physician- or patient-based satisfaction assessments. In these studies, clinical improvement ranged from 58.1% to 91%.[1,2,14,15] Considering the duration of efficacy, previous study reported that 75% and 77.8% of the subjects perceived improvement at 90 and 180 days, respectively.[15] In our study, 87.88%–100% and 90.91%–100% of the participants reported more than minimal improvement at week 10 and 16, respectively. Thus, the efficacy of HIFU, which increased over time in this study, is in line with the results of previous studies, but the overall efficacy was greater in our study. However, it must also be noted that previous studies involved single treatment sessions, whereas three treatment sessions were performed in this study.

Regarding safety, the transducer settings (focus depth and frequency) must be discussed because it determines the microcoagulation zone depth and size. To ensure safe and efficient treatment, accurate energy delivery to the target depth must be achieved. Although inter-individual variation exists, the skin thickness (epidermis, dermis, and subcutaneous tissue) at the cheeks (5–8 mm) is thickest, while that in the periorbital area (upper eyelid, 1.55– 2.48 mm; lower eyelid, 3.39–5.43 mm) and neck (2.32–3.72 mm) is the thinnest.[16–18] Therefore, theoretically, a 2.0-mm focus depth would more suitable for the treatment of periorbital, perioral, and neck skin than 3.0-mm or 4.5-mm depth probes. Nerve injury, one of the most important side effects of HIFU treatment, is caused by local heat delivered deep into the superficial musculoaponeurotic system. Areas where the facial nerve branches lie superficially (pre-auricular or perioral areas) are at higher risk of nerve injury.[2,19–21] In our study of 102 participants, no neurological AEs including nerve injury or numbness were reported, which is also a significantly lower frequency than the previous study results.[2]

Other than neurologic complications, the most common AEs are erythema, pain, bruising, or oedema, linear striations/wheals, pigmentary changes, or fat atrophy have been reported.[22–24] In this study, 36.93%, 17.61%, and 1.70% developed erythema, oedema, and pruritus, respectively. There were no cases other AEs. This result is significantly lower than that of a previous report in which all subjects developed at least trace or slight erythema and oedema immediately after treatment.1 Furthermore, the highest NRS pain scores were 0.76–2.47 immediately after the first treatment, which is significantly lower than those of previous reports (3.9–6.53).[1,25,26] Since pain is the most frequently reported discomfort related to HIFU treatment, minimizing pain is valuable for patient retention.[27]

Based on the correlation analyses, clinical improvements were more prominent in the younger age group, consistent with previous results.[28,29] This is because younger patients may respond better because as tissue ages, heat-labile collagen bonds are gradually replaced by irreducible multivalent cross-links.[30] Also, younger subjects experience a faster wound healing process.[29] On the other hand, there was no significant difference in clinical outcomes by Fitzpatrick skin type. This was expected because the absorption of ultrasound energy is independent of melanin content or skin color.

To date, we could find one study compared efficacy and safety of MFU-V with other therapeutic intervention, subsurface monopolar radiofrequency (SMRF) for neck tightening and rejuvenation.[31] In the study, both MFU-V and SMRF showed a significant decrease in the mean investigator-assessed neck laxity grade by day 90 and persistent to day 180. Subject satisfaction was identical between two groups.

This study has some limitations. First, this study had a short follow-up period of 16 weeks. Second, 90% of the enrolled participants were Korean. Finally, although we included various objective measurements, the study lacked a histological analysis. Despite these limitations, we believe that the relatively large sample size, evaluation of three different areas of the face and neck, and inclusion of objective measurements strengthens our findings.

In conclusion, significant improvement in periorbital, perioral, and neck wrinkles was observed using a HIFU device with a 5.5-MHz transducer with 2.0-mm focal depth. Therefore, further well-designed controlled studies with more participants of various ethnic backgrounds, histological evaluations, and long-term follow-up will be necessary to establish more effective optimal treatment parameters.

## ACKNOWLEDGMENTS

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## AUTHOR CONTRIBUTIONS

Hye Sung Han: Conceptualization, methodology, original draft, investigation. Jae Wan Park: Validation, investigation, original draft. Soo Yeon Kim: Validation, investigation, supervision. Kwang Ho Yoo: Review and editing manuscript, investigation, supervision. Sun Young Choi: Conceptualization, methodology, review and editing manuscript. Beom Joon Kim: Conceptualization, methodology, review and editing manuscript.

## DATA AVAILABILITY STATEMENT

Research data are not shared.

## ORCID

Hye Sung Han
https://orcid.org/0000-0002-3556-0740
Jae Wan Park
https://orcid.org/0000-0003-2690-6495
Kwang Ho Yoo
https://orcid.org/0000-0002-0137-6849
Beom Joon Kim
https://orcid.org/0000-0003-2320-7621

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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# Vulvar Rejuvenation Using High-Intensity Focused Ultrasound (HIFU): Fundamentals and Technique

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Isabelle Maria Almeida e Benevides[3] | Adriele Machado Dantas[3] | Thiago Gusmão da Silva[4]
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Thiago Gusmão da Silva[4] | Carolina Barreto Ribeiro Martins dos Santos[5] | Brazil

[1]Estácio de Sá University, Rio de Janeiro, Brazil
[2]IDE Faculty—Institute for Educational Development, Salvador, Brazil
[3]Longevitat Clinic—Advanced Aesthetics, Salvador, Brazil
[4]FAINOR, Independent College of the Northeast, Vitória da Conquista, Brazil
[5]UFBA, Federal University of Bahia, Salvador, Brazil
Email:*fabioborges2000@gmail.com

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## Abstract

**Background:** The unaesthetic appearance of the female intimate area (vulva, “mound of venus” and perianal region) is a triggering factor of negative psychological responses, embarrassment, anxiety and insecurity in many women. Using rejuvenating equipment for vaginal structure or for the intimate area as a whole is already widespread in the literature, and High-Intensity Focused Ultrasound (HIFU) has proven to be very effective in the clinical practice of many professionals. This study, therefore, aims to describe the fundamentals and applicability that guide the use of HIFU in vulvar rejuvenation.

**Materials and Methods:** Exploratory research was carried out, presented in a narrative review, to highlight the action of HIFU in female intimate rejuvenation. The review explored scientific articles published and available in the following databases: MEDLINE (Medical Literature Analysis and Retrieval System Online), PubMed (National Library of Medicine), SCIELO (Scientific Electronic Library Online), and LILACS (Latin Literature American and the Caribbean in Health Sciences). In addition, some clinical findings obtained through a retrospective analysis of medical records were added to describe the authors’ clinical experience in the use of Focused Ultrasound (HIFU) for vulvar rejuvenation.

**Results:** We verified that the tissues of female external genitalia respond very well to the stimuli of the focused sound waves of the HIFU, being able to produce immediate and lasting results through isolated applications or in association with intradermotherapy or other therapeutic resources.

**Conclusion:**
We conclude that using High Intensity Focused Ultrasound aimed at vulvar rejuvenation is safely indicated and assures excellent aesthetic results at the end of the treatment because similarly to other treatment techniques, the thermal stimuli of HIFU are also able to produce an excellent therapeutic response in the dermal tissue of the female intimate area, promoting intense neocollagenesis and generating great aesthetic improvement.

## Keywords

Intimate Aesthetics, Vulvar Rejuvenation, Vaginal Rejuvenation, HIFU, Focused Ultrasound, Micro Focused Ultrasound, and Cosmetic Gynecology

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## 1. INTRODUCTION

Currently, there has been an increase in demand for aesthetic procedures able to treat the female intimate region. However, for some women, the desire for these therapies is still complex since it can affect various physical and psychological aspects of the woman's life. Therefore, aesthetic alterations resulting from the natural aging process or aggravated by external factors related to daily life habits (smoking, excess alcohol, use of medication), as well as those from vaginal delivery childbirth, surgical sequelae, physiological changes resulting from a lifetime sexually active, sports (such as cycling) and others, are part of the daily lives of professionals who work in the treatment of aesthetic dysfunctions of the female intimate region.

It is important to mention there is no pre-established beauty standard for the female external genitalia, but what pleases or bothers the woman. Thus, it is understood that the unpleasant aesthetic appearance of the female intimate region (vulva, "mound of venus", perianal region, etc.) is a relevant point in cases of increased negative psychological responses, embarrassment, anxiety and insecurity[1]; therefore, this can guide the search for treatment of the intimate area and the choice of the most effective therapeutic resource for each case (essential for rescuing female self-esteem), since that sometimes the visual aspect and functionality of the introitus are marked in the majority sometimes as responsible for sexual disorders and reduced quality of life[2].

The use of rejuvenating equipment including the intimate area is already widespread in the literature, for instance, mainly radiofrequency (RF), which through an increase in temperature promotes stimuli at the cellular level capable of promoting an improvement in the quality of the vulvar tissue [3,4]. High Intensity Focused Ultrasound (HIFU) was initially described as a non-invasive treatment for facial sagging, as it has the ability to reach deeper tissues without damaging the epidermis, by the production of small controlled thermal coagulation points in the reticular dermis medium and/or deep, being able to reach even the superficial muscular aponeurotic system (SMAS), might generate an immediate contraction/retraction of the thermally denatured collagen, initiating a neocollagenesis and the remodeling of the collagen with subsequent cutaneous tissue stiffening in a non-invasive way[5].

HIFU can induce neocollagenesis in the middle and lower reticular dermis, and neoelastogenesis in the deep reticular dermis. In a comparative study between monopolar radiofrequency and HIFU[6], the authors have concluded that RF affects tissue more diffusely while HIFU causes more focal collagen induction.

Currently, the use of HIFU in the intimate area has already been described by several authors[7,8,9] with the aim of treating vaginal atrophy and laxity, urinary incontinence, non-surgical vaginoplasty and other conditions; however, no consistent reports were found associating the use of high-intensity focused ultrasound for the aesthetic rejuvenation of the external genitalia.

Afterall, this study aimed to describe the fundamentals that guide the High- Intensity Focused Ultrasound utilization in vulvar rejuvenation presenting data about fundamentals that direct its use in an effective and safe way as well as the findings obtained by the clinical practice of the authors.

## 2. Materials and Methods

This study is characterized by exploratory research written as a narrative review to highlight the action of high-intensity focused ultrasound (HIFU) in vulvar rejuvenation. The review explored scientific articles, published and available in the following databases: MEDLINE (Medical Literature Analysis and Retrieval System Online), PubMed (National Library of Medicine), SCIELO (Scientific Electronic Library Online) and LILACS (Latin American and Caribbean Literature in Health Sciences).

As inclusion criteria, it was selected sources that mentioned aesthetic condition of the female intimate area or described the fundamentals of using HIFU related to skin rejuvenation and toning. Sources that did not present the abstract, were not allocated in scientific journals and did not address the subject of the study. Also, the same for those that did not support the collection of reliable data, were discarded.

The bibliographic survey was carried out in Portuguese and English, with the following descriptors: Intimate aesthetics, vulvar rejuvenation, vaginal rejuvenation, HIFU, focused ultrasound, micro focused ultrasound, and cosmetic gynecology.

In addition to the bibliographic review, some treatment protocols for vulvar rejuvenation were added to this work based on authors clinical practice using high-intensity focused ultrasound, associated or not with other therapeutic resources.

## 3. Results and Discussion

High Intensity Focused Ultrasound (HIFU) was developed for a non-surgical treatment, aiming at skin retraction by stimulating the creation of new collagen and elastin[10].

HIFU is a device designed to produce small microthermal zones of coagulation in the middle reticular layer, the deepest of dermis and subdermis (SMAS), leading to a wound healing response leading to tissue contraction and new collagen production or reduction of adiposities and cellulite[11, 12]. Local absorption of energy causes intermolecular vibration and produces heat (over 65˚C), enough for collagen denaturation at thermal coagulation points (TCP) (approximately 1 mm3 to 1.5 mm3)[13].

From the thermal injury the tissue repair process begins. According to some authors[14], the evolutionary healing process from 48 hours post-injury occurs as follows: 1) From the first 48 hours to 10 weeks after treatment: Inflammation stimulates fibroblast proliferation, neocollagenesis and elastogenesis around TCPs; 2) On the 28th day: adjacent dermis undergoes remodeling and viscoelasticity increases; 3) Over time, the skin becomes thicker and tenser, further increasing the elastin in the injured area and the collagen in the reticular dermis; 4) 10 weeks after treatment: Collagen is completely replaced in the treated areas, there is greater tightening and lifting of the skin—this remodeling may last up to a year.

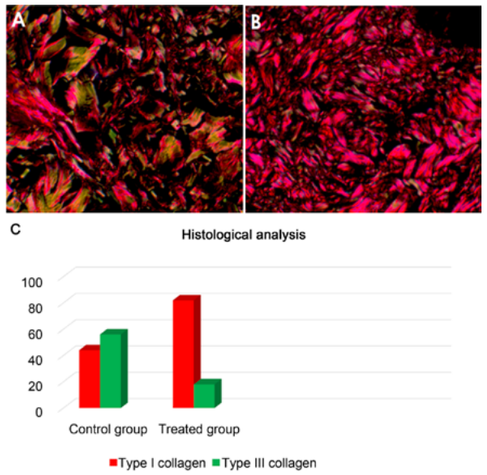


**Figure 1** Histological analysis (A) Control Group with type III collagen predominance (green—56%); (B) Group treated with expressed increase of type I collagen (orange color—82%), when compared to type III collagen (green—18%); (C) Comparative graphic (Source: Meyer et al . (2021) [15]—Reproduced with authorization.).

Authors[15] found that 45 days after treatment there was already an evident increase in the number and size of fibroblasts in the treated group, as well as a greater number of blood vessels and inflammatory cells compared to the control group. Also, they found that there was already an evident rising in collagen type I compared to collagen type III (Figure 1).

Although the literature commonly describes a late effect on skin components and an improvement in the aesthetic appearance after the use of HIFU, in our clinical practice we identify immediate effects on the skin, both in facial treatments (Figure 2) and in treatments of the intimate area (Figure 3). The reason for these findings is the thermal action of HIFU on the fibrous tissue constituting the SMAS ("lifting effect"), as well as on the collagen of the reticular dermis[10, 16, 17].

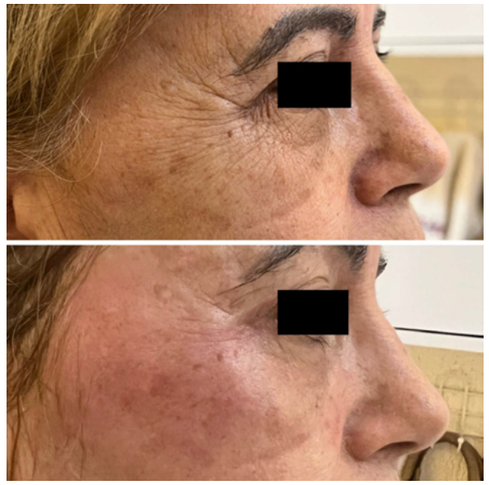

**Figure 2** Immediate effect of High Intensity Focused Ultrasound in the periorbicular region of the eyes (7 Mhz - 3.0 mm and 10 Mhz - 1.5 mm transducers were used - Ultramed® manufactured by Medical San Ind Equipment's Med, Brazil.).

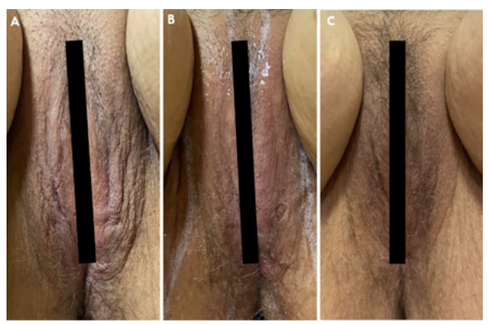


**Figure 3** (A) Vulvar region before treatment; (B) Immediate effect of high intensity focused ultrasound; (C) Late aesthetic effect, 40 days after 1 treatment session (7 Mhz - 3.0 mm and 1.5 mm transducers were used—Ultraformer III® manufactured by CLASSYS INC., Seoul, Korea.).

Despite the remarkable immediate effect on the skin, HIFU has proven to be even more efficient in the long term. Authors[18] reported that the interval for a reevaluation, in order to judge the results, may vary from 2 to 6 months; however, Suh et al . (2016)[19] treated individuals with a total of 3 sessions of Focused Ultrasound with intervals of 4 weeks between sessions.

Based on these reports, in our clinical practice we have been suggested that clients return for reassessment 30 or 40 days after the procedure (especially when the immediate effects on the skin in the intimate area are not so evident) in order to reassess them for evaluating whether the initially proposed treatment plan should be maintained or changed according to the results obtained after this period. Corroborating and justifying the clinical practice of the authors of the present study, Ko et al . (2017) [20] reassessed skin elasticity in individuals treated with HIFU 4 and 12 weeks after 1 treatment session. Authors also reported that there was a significant improvement in the first reassessment (4 weeks) after HIFU treatment, and when reassessing the same individuals again 12 weeks after treatment they did not identify significant changes in elasticity improvement compared with what was verified in the first revaluation.

In our cases of vulvar rejuvenation care where no apparent result was obtained, 30 or 40 days after the consultation, it was evaluated the possibility of associating other therapeutic resources such as electrotherapy and/or intradermotherapy was to assure and/or enhance the results. In Figure 3 and Figure 4, it is possible to visualize the satisfactory evolution after 40 days of the initial treatment for vaginal rejuvenation.

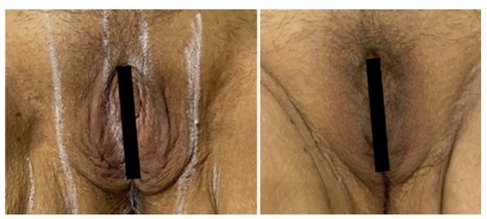

**Figure 4** Late aesthetic effect, 40 days after 1 treatment session with High Intensity Focused Ultrasound (7 Mhz - 3.0 mm and 1.5 mm transducers were used—Ultraformer III® manufactured by CLASSYS INC., Seoul, Korea.).





In line with our clinical practice, we recommend the use of 3.0 and 1.5 mm transducers for vaginal rejuvenation combined in each treatment session. Nonetheless, other forms of application have been seen in the intimate rejuvenation market, and these use depths of 2.0 mm and even 4.5 mm.

In line with our clinical practice, we recommend the use of 3.0 and 1.5 mm transducers for vaginal rejuvenation, combined in each treatment session. However, other forms of application have been seen in the intimate rejuvenation market, and these use depths of 2.0 mm and even 4.5 mm.

Based on the study by Oni et al. (2014)[21], the number of TCP lines suggested for the treatment of the external part of the intimate area is, on average, 20 to 30 lines on each side (Figure 5), for each depth. Usually, 40 to 60 lines are achieved in total when using only two transducers without the Vertical Vectoring technique.

Some authors recommended the overlapping of lines of TCPs, the Vertical Vectoring technique[22,23] (also popularly called the "Hashtag" technique). That technique consists of performing lines of TCPs in the horizontal and vertical directions, overlapping them in the same treated region and increasing the number of points deposited. An advantage of this approach is the possibility of using lower energies and generating more comfort for the client without prejudice to the contraction of skin collagen, due to the greater number of TCPs per region.

Currently, we have consistently applied Vertical Vectoring for vulvar rejuvenation, using 3.0 mm and 1.5 mm transducers with safety and good results (Figure 6 and Figure 7).

The distance between the lines of TCPs ranges from 2 to 5 mm [18]. This might be adjusted to make with it occurs automatically during the delivery of TCPs using "multiline" transducers, but with the use of "single-line" transducers. This procedure is characterized as operator-dependent and it will require the professional's dexterity so that there is no damage to the results due to the non-uniformity in the delivery of TCP lines. In our clinical practice, we try to distance the lines by about 3 millimeters between them.

According to Lee et al . (2012)[24], the spacing between

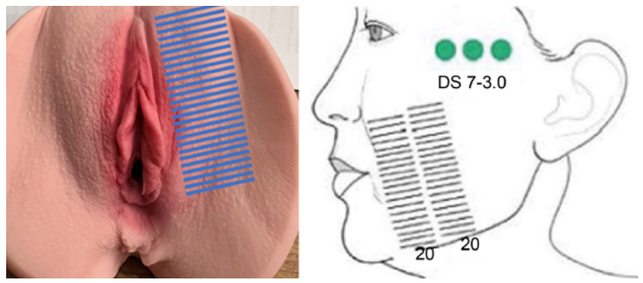


**Figure 5** Scheme illustrating line distribution of HIFU TCPs for vaginal rejuvenation (Adapted from Oni et al ., 2014[21]).

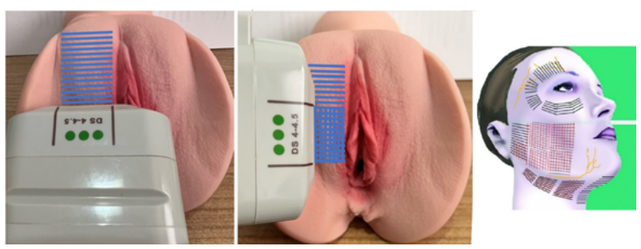

**Figure 6** Scheme illustrating the distribution of lines of HIFU TCPs with the Vertical Vectoring ("Hashtag") technique for vulvar rejuvenation. (Adapted from Werschler & Werschler, 2016[22]).

thermal coagulation points must be related to depth. Thus, a distance of 1.5 mm between the points must be adjusted in the equipment when energy is supplied at a depth of 4.5 mm; 1.1 mm distance between points when power is supplied at a depth of 3.0 mm. For Jeon et al . (2018)[25], cartridges with depths of 1.5 mm and 3.0 mm should be used with a distance between points of 1.2 mm.

In the treatment of aesthetic dysfunctions, both on the face and on the external genitalia, considering that we primarily use depths of 3.0 mm and 1.5 mm we recommend 1.2 mm as the ideal distance between TCPs. If the client complains that these parameters are very uncomfortable, it is possible to reduce or increase the distance between the clotting points to 1.3 to 1.5 mm.

With regard to the energy dose (Joules) used, there is difficulty in standardizing it due to the fact only one model of equipment was used in our clinical practice and teaching, and thus, we recommend that the dose be compatible, initially, as the customer's tolerance level. Therefore, the professional can use dose control measures such as directly decreasing the energy and/or increasing the distance between the TCPs. There are clients who cannot tolerate pain and may need medication to alleviate their discomfort.

Working in the intimate area with HIFU revealed a problem for some professionals regarding antisepsis measures and/or degerming the transducer after use (autoclaving is not recommended for transducers since their structure contains many electronic components that could be damaged once exposed to high temperatures). In view of this, with the aim of reducing the risk of disease transmission among clients through the "shared use" of the transducer, an efficient measure to be adopted is to use a sheet of plastic film over the wave sound emission area of the transducer (to avoid contact of the device with the external genital structure (Figure 8). It is important to highlight that it is extremely important to use a good layer of common gel between the transducer and the plastic film when preparing it for application. And, after its use, it must be discarded.

Finally, we emphasize the importance of High Intensity Focused Ultrasound (HIFU) associations with other resources mainly with intradermotherapy techniques. In traditional applications, especially on the face, collagen biostimulators already find support in the literature [26,27] and products based on calcium hydroxyapatite are becoming very known in clinical practice of many professionals [11,28,29,30], as well as hyaluronic acid [31] and polylactic acid [32].

For vulvar rejuvenation, in our clinical practice we have also been using collagen biostimulators from the Brazilian industry (sterile base products for multipurpose use in the aesthetics segment) that are composed of several active ingredients which ones have a potentiating action to increase dermal collagen. Figure 9 and Figure 10 show some effects of associating of HIFU with some biostimulators.

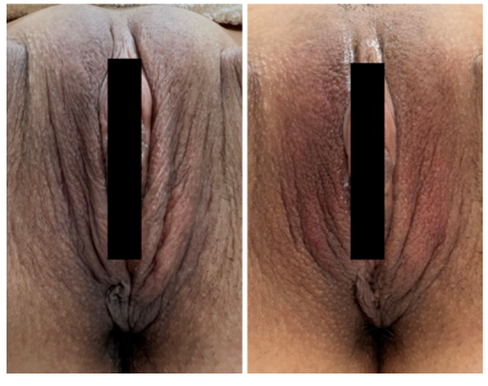

**Figure 7** Immediate effect of using the Vertical Vectoring ("Hashtag") technique in vulvar rejuvenation, using 7 Mhz - 3.0 mm and 1.5 mm transducers (Total of 68 TCP lines with each transducer.) (Ultraformer III® manufactured by CLASSYS INC., Seoul, Korea.).

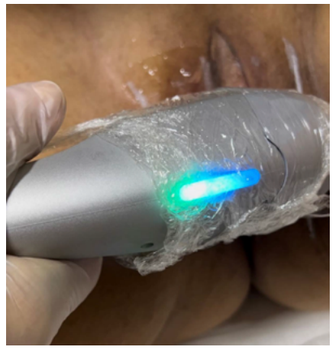

**Figure 8** Protection of the HIFU transducer with plastic film for use in the intimate area.





## 4. Conclusions

This study shows that the conventional applicability of High Intensity Focused Ultrasound, both on the face and body, might be replicated in vulvar rejuvenation treatments with guaranteed safety and efficacy.

Furthermore, it is notorious that, just as radiofrequency, fractional laser or plasma jet produce an excellent therapeutic response in the skin in the female intimate area, the thermal stimuli produced by the use of HIFU are also able to promote intense neocollagenesis in the dermal tissue, i.e ., guarantees an excellent vulvar rejuvenation response and improves the aesthetic appearance of the region. Additionally, we identified that the association of collagen bio stimulating products is fully indicated when the aim is to enhance the production of dermal collagen in the intimate area.

Finally, we conclude that the use of High Intensity Focused Ultrasound is a promising, safe and extremely effective adjuvant alternative to support the treatment of unsightly conditions in the female intimate region.

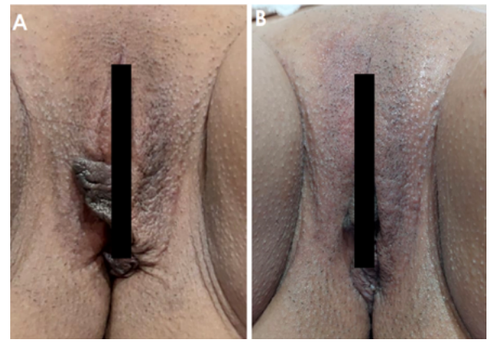


**Figure 10** Association of focused ultrasound with collagen biostimulator: (A) Before treatment; (B) Immediate effect of HIFU (Ultramed® manufactured by Medical San Ind Equipment's Med, Brazil.) associated with the injection of Flacidez® (Mezzo Ind Cosmetics, Brazil.).

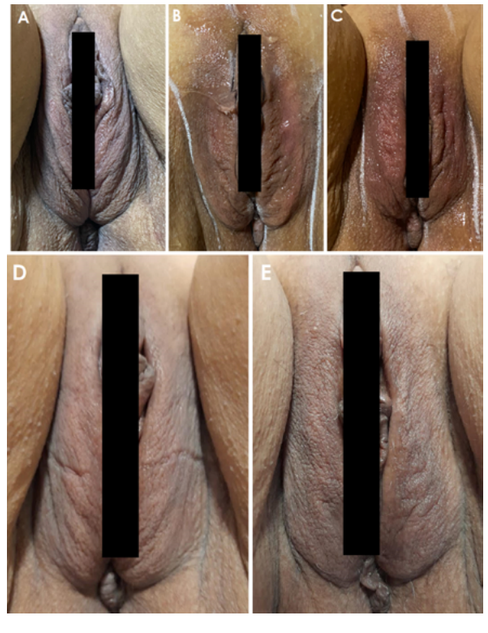


**Figure 9** Association of Microfocused Ultrasound with collagen biostimulator: (A) Before treatment; (B) Immediate effect of HIFU (Ultraformer III® manufactured by CLASSYS INC., Seoul, Korea.); (C) Right after the injection of Sculpt Derm Collagen Booster® (Cosmobeauty Ind Com Cosmetics, Brazil.); (D) 45 days after the 1st treatment session; (E) 90 days after treatment.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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# The Efficacy of High-Intensity Focused Ultrasound Treatment for Sagging Upper and Lower Eyelids

Giovanna Ignacio, MD By Kevin A. Wilson, Contributing Editor

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## Vulvar Transformation with Ultraformer III Micro- and Macrofocused Ultrasound

Giovanna Ignacio, MD By Kevin A. Wilson, Contributing Editor | Brazil

Non-invasive micro- and macrofocused ultrasound (MMFU) with the Ultraformer III platform from Classys, Inc. (Seoul, Korea) is designed to stimulate collagen remodeling to lift, tighten and recontour skin of the face and body. Its high peak power, rapid and precise shot application, and combination of high and low frequency ultrasound give it versatility but keep comfort high and downtime low. With these capabilities, one can also treat the external female genitalia to return lax and redundant tissue to a more youthful and functional state. MMFU is the core technology of Ultraformer III. According to Giovanna Ignacio, MD, a cosmetic gynecology specialist in Brazil, “Macro TCP (thermal coagulation point) can induce fat reduction, whereas using Micro TCP, the dermal layer environment is improved by using a cartridge that targets it specifically. Patients may feel quite dry immediately following the procedure, but after recovery the dermal layer becomes firmer through collagen remodeling, which can improve dryness.

“I often use Ultraformer III for vulvar tissue sagging, clitoral hood phimosis, and mons pubis lipodystrophy (pubic mound fat),” Dr. Ignacio continued. “Female cosmetic genital surgery is not new, but today patients are looking for treatments that do not require downtime.”

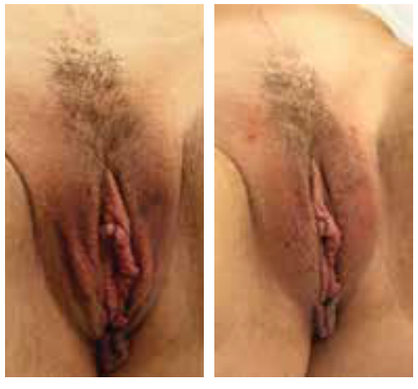

**Figure 1** Before and after treatment with Ultraformer III

For the female genitalia, Ultraformer III treatment appeals to those seeking an effective but low downtime option to minimize the impact on their day-to-day lives.

“After the age of 40, women enter a phase of hormonal decline and this accelerates the sagging of the whole body, including the vulva,” Dr. Ignacio explained. “This treatment is useful for younger women who want to improve their self-esteem and self-confidence in their relationships. Most patients who visit the clinic have concerns about the flaccidity of the area, but the technology also helps patients who feel uncomfortable due to dryness. While we have many options when it comes to treating that specific area, Ultraformer III has no restrictions on treatment, and no preor post-treatment care is required.

“CO2, Er:YAG and thulium lasers are typically used for ablation in vulvar treatment,” Dr. Ignacio added. “Although the effect can be more dramatic, patients have a hard time enduring the recovery period. There may be a risk of infection while the wound heals, which takes longer in older patients.” Likewise, in the case of surgery the incision must be closed, requiring even more care and recovery time. “With Ultraformer III there is no excision of the treatment area, so the procedure itself is more comfortable,” Dr. Ignacio pointed out. “It targets the dermis and does not harm the epidermis, so it is convenient to use with other treatments.”

Ultraformer III is convenient for the user as well; nevertheless Dr. Ignacio cautions that you should be a qualified medical personnel who can adjust treatment based on the individual and anatomical location. Cartridge sizes range from small to large, the large being most useful when treating the pubic area, according to Dr. Ignacio. “This advantage is one of the reasons why I always choose Ultraformer III to treat my patients. Different generations of the device are used all over the world, so we are confident that it is safe. The possibility of side effects and discomfort are reduced as it has a narrow contact surface to minimize side effects and reduce pain.”

# Tightening and Reduction of Unwanted Submental Fat Using Triple-Layer High-Intensity Focused Ultrasound: Clinical and 3-Dimensional Imaging Analysis

Hyuck Hoon Kwon, MD, PhD | Steven Hoseong Yang, MD, PhD | Mira Choi, MD, MS
Jae Yoon Jung, MD, MS | Gyeong-Hun Park, MD, PhD§



## Tightening and Reduction of Unwanted Submental Fat Using Triple-Layer High-Intensity Focused Ultrasound: Clinical and 3-Dimensional Imaging Analysis

Hyuck Hoon Kwon, MD, PhD | Steven Hoseong Yang, MD, PhD | Mira Choi, MD, MS
Jae Yoon Jung, MD, MS | Gyeong-Hun Park, MD, PhD§ | South Korea

**Background:** Unwanted submental fat (SMF) is aesthetically unappealing, but methods of reduction are either inva or lack evidence of their use.
**Objective:** The authors sought to evaluate the safety and efficacy of a novel triple-layer high-intensity focused ultrasound (HIFU) regimen for SMF reduction.
**MEethode:** Forty Korean subjects with moderate/severe SMF were evaluated after receiving a session of triple-layer HIFU treatments (using 3.0-, 4.5-, and 6.0-mm focusing transducers). The objective evaluation based on the 5-point Clinician- Reported Submental Fat Rating Scale (CR-SMFRS) and patients' satisfaction based on the 7-point Subject Self-Rating Scale (SSRS) were determined 8 weeks after treatment. Three-dimensional image analysis was also performed.
**Results:** At the follow-up visit, the proportion of treatment responders defined as subjects with $1-point improvement in CR-SMFRS was 62.5%, and the proportion of patients satisfied with appearance of their face and chin (score $4 on the SSRS) was 67.5% of the total patients. The results of 3-dimensional analysis were consistent with clinical observations. Only mild and transient side effects were observed for some patients with no serious adverse effects.
**Conclusion:** The triple-layer HIFU regimen including the novel 6.0-mm transducer has benefits for tightening and rejuvenation of the area with unwanted SMF, showing reasonable safety profiles.

Accumulation of subcutaneous fat in the pre- plastysmal area, undesirable submental fat (SMF), can lead to the loss of lower facial contour and mandibular definition.1 This condition gives the appearance of obesity and aging, and it has been shown to contribute to negative aesthetic and psychological effects.[2,3] Although this cosmetic indication can be addressed surgically as part of platysmaplasty or liposuction,[4] patients' concerns regarding prolonged downtime and the invasive nature limit the popu- larity of these procedures. Therefore, nonsurgical energy de- vices, including cryolipolysis, radiofrequency, and high- intensity focused ultrasound (HIFU), and mesotherapy with deoxycholic acid or phosphatidylcholine have received much attention for dealing with these localized adipose tissues.5–7

High-intensity focused ultrasound has been widely applied as a novel treatment modality for skin tightening and rejuvenation with superior safety profiles.[8] It produces small, microthermal lesions at precise depths up to the fibromuscular layer, causing thermally induced tissue contraction and coagulation with subsequent collagenesis.[9,10] Two conven- tional HIFU transducers (7 MHz, 3.0-mm focal depth and 4 MHz, 4.5-mm focal depth) have been used in the treatment of the face and neck, but a transducer with a lower frequency and deeper focal depth (2 MHz, 6.0 mm) also demonstrates satisfactory results for the treatment of skin and subcutaneous fat in certain body areas.[11,12]

Anatomically, SMF is a discrete areolar chamber residing within the preplatysmal fat bounded superficially by the dermis and deeply by the platysma.[13,14] Considering anatomic characteristics of SMF and lipolytic traits of a deeply penetrating transducer, the authors expected that the addition of a 6.0-mm transducer to the conventional treatment regimen could further contribute to reduction of subcutaneous fats and tightening of adjacent tissues. In this study, the authors evaluated the efficacy and safety of a triple-layer HIFU regimen including a novel 6.0-mm transducer for reduction of SMF by applying 3-dimensional (3D) analysis technology.

From the *Oaro Dermatology Clinic, Seoul, Republic of Korea; † Guam Dermatology Institute, Guam; ‡ Department of Dermatology, Ilsan Paik Hospital, Inje University College of Medicine, Goyang, Republic of Korea; § Department of Dermatology, Dongtan Sacred Heart Hospital, Hallym University College of Medicine, Hwaseong, Republic of Korea The authors have indicated no significant interest with commercial supporters.
J. Y. Jung and G.-H. Park contributed equally as corresponding authors.
Address correspondence and reprint requests to: Gyeong-Hun Park, MD, PhD, Department of Dermatology, Dongtan Sacred Heart Hospital, Hallym University College of Medicine, 7, Keunjaebong-gil, Hwaseong-si, Gyeonggi-do 18450, Republic of Korea, or e-mail: borelalgebra@gmail.com Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.dermatologicsurgery.org).
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## SUBJECTS AND METHODS

### SUBJECTS

Forty Korean subjects completed this study (Table 1). Subjects were eligible to participate if they presented with moderate to severe SMF (Grade 2 or 3 on the 5-point Clinician-Reported Submental Fat Rating Scale [CR-SMFRS]) and expressed dissatisfaction with the appearance of their submental area (Subject Self-Rating Scale [SSRS] score 0 to 3) (See Supple- mental Digital Content 1, Table S1, http://links.lww.com/DSS/A916).15 Key exclusion criteria included pregnancy, a history of keloidal scarring, and cosmetic surgery or rejuvenation procedures within 6 months before the study. Patients with a body mass index .35 kg/m2 and those undergoing or considering a weight reduction program were also excluded. All patients were informed of the benefits, risks, and possible complications of the treatment before enrolment, and in- formed consent was obtained from each participant. Protocol of this study conformed to the ethical guidelines of the Declaration of Helsinki (1975) and was approved by the Institutional Review Board.

### TREATMENT PROTOCOL

One HIFU device (Shurink/Ultraformer; Classys, Inc., Seoul, Korea) was used in this study. The authors used 3 different types of transducers (T2: 3.0-mm focal depth, T3: 4.5-mm focal depth, and T4: 6.0-mm focal depth). Each transducer delivered a series of ultrasound pulses along 25- mm-long exposure lines. The pulse duration for each individual exposure ranged from 25 to 40 milliseconds.

All patients received one designated session of HIFU. Before treatment, submental areas were cleansed with a mild soap, and topical anesthesia with EMLA (Astrazeneca, So¨derta¨lje, Sweden) was applied to the SMF under 30- minute occlusion. After gently removing the anesthetic cream, ultrasound gel was applied to the skin. The probe was then placed firmly on the skin surface with uniform pressure. To avoid possible damage to the marginal mandibular nerve, the space within 1.0 cm along the mandibular borderline was spared from treatment. Sub- mental fat was treated with 80 lines of 6.0-mm probe at an energy setting of 0.8 to 1.0 J, immediately followed by 60 lines of 4.5-mm probe at 0.5 to 0.7 J, then finally by 60 lines of 3.0-mm probe at 0.3 to 0.5 J (Figure 1). The spacing of pulses within each linear array was set parallel at 1.5–2.0 mm. On average, a total of 200 lines to the SMF were delivered. The treated areas were then soothed by cooling packs for 10 minutes. After finishing the protocol, 33 subjects were reinterviewed by phone or email. They were asked about their SMF status 6 to 8 months after the procedure. In addition, 1 participant visited again and took pictures under the same conditions.

### OUTCOME EVALUATIONS

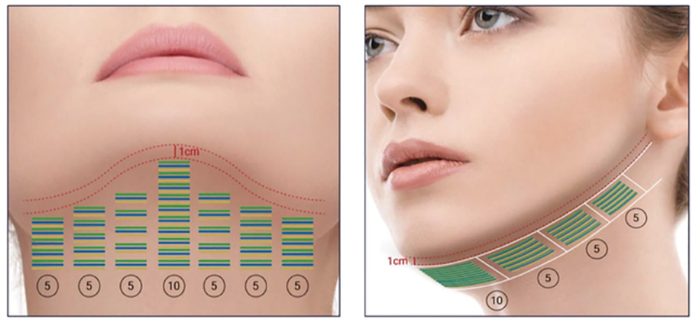
Follow-up visits took place 8 weeks after the treatment session. Improvement was defined as the proportion of treatment responders, that is, with a reduction in SMF of $1 point on the 5-point CR-SMFRS compared with baseline, and the proportion of patients satisfied with their appear- ance in association with their face and chin (i.e., with a score of $4 on the 7-point SSRS rating scale). Clinician-Reported Submental Fat Rating Scale was determined by 2 derma- tologists evaluating paired baseline and follow-up photo- graphs of the 40 patients in a randomized fashion. Photographic documentation using the same camera settings (EOS 600D; Canon, Tokyo, Japan) and lighting conditions was obtained at each visit. Pain sensation during treatments was reported using a 0-to-10 visual analogue scale (VAS) score (0: none; 10: extremely severe).16 Treatment-related adverse effects were characterized de- scriptively at each visit.

| | Subjects, n 5 40 |
|---|---|
| Age, mean (SD), yr | 40.5 (11.0) |
| Female, n (%) | 38 (95.0) |
| Race | All Korean patients |
| BMI, mean (SD), kg/m2 | 23.8 (3.2) |
| SMF grade by CR-SMFRS, n (%) | Grade 2: 16 (40%), Grade 3: 24 (60%) |
| Fitzpatrick skin type, n (%) | III: 15 (37.5%), IV: 20 (50.0%), V: 5 (12.5%) |
| BMI, body mass index; CR-SMFRS, Clinician-Reported Submental Fat Rating Scale; SMF, submental fat. | |

**Table-1** Demographic and Baseline Characteristics








Frontal view Lateral view

**Figure 1** Triple-layer high-intensity focused ultrasound regimen for unwanted submental fat (green: 3-mm transducer, blue: 4.5-mm transducer, gold: 6.0-mm transducer).

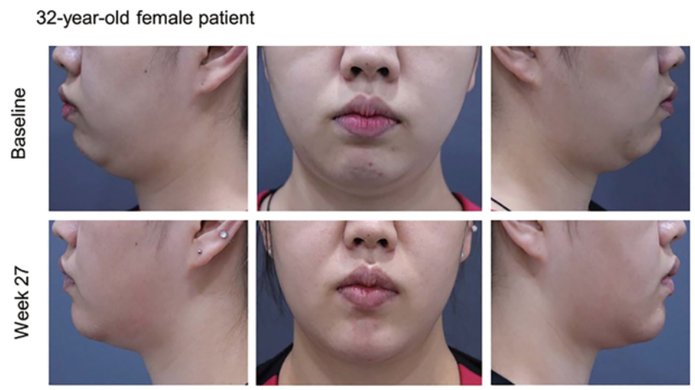
## THREE-DIMENSIONAL MEASUREMENT

To provide supportive data for the objective evaluation of treatment results, a 3D camera and software (Morpheus Co., Ltd., Seongnam, Gyeonggi-do, Korea) were used for 20 patients. Images taken were imported into Mirror Analysis 3D software and registered using anatomical landmarks for proper alignment. Topographical changes gained after superimposition of multiple pictures provided complemen- tary data. Surface area reduction of SMF was also measured on 3D photographs.

## RESULTS

### CLINICAL EFFICACY

At the follow-up visit, the proportion of treatment responders ($1 point improvement in the 5-point CR-SMFRS) based on objective evaluation was 62.5% (25/40) of all enrolled patients. Ten patients (25.0%) experienced more remarkable improvement ($2-point improvement in CR-SMFRS) only with a single HIFU session. The pro- portion of patients satisfied with the appearance of their face and chin after treatment (score $4 on the 7-point SSRS) was 67.5% (27/40) of all enrolled patients. Photographs of representative patients treated with the triple-layer tech- nique of HIFU are shown in Figures 2 and 3. Lateral views clearly




| | Weight(kg) | CRSMFRS | SSRS |
|---|---|---|---|
| Baseline | 58.3 | 3 | 1 |
| Week 27 | 57.9 | 1 | 6 |

**Figure 2** A 32-year-old woman treated with one session of triple-layer high-intensity fo- cused ultrasound regimen for her unwanted submental fat. CR-SMFRS, Clinician-Repor- ted Submental Fat Rating Scale; SSRS, Sub- ject Self-Rating Scale.


| | Weight(kg) | CRSMFRS | SSRS |
|---|---|---|---|
| Baseline | 65.3 | 3 | 1 |
| Week 8 | 65.1 | 2 | 5 |

**Figure 4** A 63-year-old woman treated with one session of triple-layer high-intensity fo- cused ultrasound regimen for her unwanted submental fat. CR-SMFRS, Clinician-Repor- ted Submental Fat Rating Scale; SSRS, Sub- ject Self-Rating Scale.

demonstrated that cervicomental angles decreased remarkably after HIFU treatments. At 6 to 8 months after the procedure, 33 subjects were interviewed again by phone or email. Most of them (73%) replied that their SMF status remained improved compared with baseline.

## THREE-DIMENSIONAL IMAGE DATA ANALYSIS

The volume map of a fusion of 3D images before and after treatment further validated the volume loss of SMF as a result of skin tightening and lipolysis (Figure 4). In all 20 patients participating in 3D image analysis, topographical changes and designated area maps indicated a decrease in SMF to varying degrees. Topographical color maps commonly showed that the lower part of SMF decreased more than the upper part. On average, 7.7% 6 1.7% (mean 6 SE) of SMF surface area was decreased after one session of HIFU treatment.

## SAFETY PROFILES

During treatments, patients felt only minimal pain, with an average VAS of 3.3. No patient reported severe pain requiring oral medication for analgesia or sedation. Eleven patients (27.5%) had mild erythema that persisted less than 1 day. Other mild posttreatment signs also disappeared soon after. There were no serious adverse events such as persistent scar,

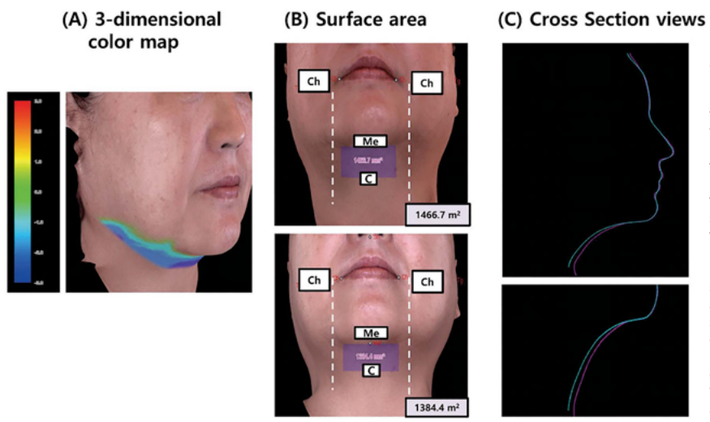



**Figure 4** Three-dimensional image analysis before and after a high-intensity focused ultrasound (HIFU) treatment session. (A) In the superimposed image views, topographical changes in the baseline picture compared with that of the follow-up visit are colored. As dictated in the diagram, yellow indicates areas where the vertical height of the skin surface was increased compared with baseline image, and blue indicates areas where the height was lower, which indicates a decrease in submental fat. (B) Submental surface area designated by the rectangle surrounded by vertical lines of 2 cheilion (Ch) points and horizontal lines of soft tissue menton (Me) and cervical (C) points. (C) Cross-sectional views of a patient's face before (purple) and after (blue) HIFU treatments.





bruising, or prolonged numbness. Detailed information on safety profiles is described in Table 2. All patients were able to return to their usual activity just after treatment.

## DISCUSSION

The number of noninvasive procedures is constantly growing in cosmetic dermatology. Compared with other devices or mesotherapies, HIFU demonstrates superiority in safety profile since it provides focused ultrasonic ablation energy only to the designated depth without affecting adjacent tissues.8,17 Although unwanted SMF is a major aesthetic concern, conventional HIFU trans- ducers may not fully cover the deeply located preplatys- mal fat. Considering that deeper-depth focusing transducers effectively reduce subcutaneous body fat, the authors applied the novel triple-layer HIFU regimen including a 6.0-mm transducer for the treatment of unwanted SMF.

The results of this study demonstrated satisfactory efficacy of this triple-layer regimen for SMF. More than 60% of the enrolled patients subjected to only a single session showed improvements from the perspectives of investigator-reported and patient-reported evaluations, which was consistent with the results of 3D image analyses. These results strongly suggest that this technique is at least comparable with other conventional devices or injections for the treatment of SMF.5–7,15,18 The safety profile demonstrated only slight and transient posttreatment side effects and mild pain for most patients, which supports the superior advantages of HIFU compared with other treat- ment approaches.5–7,15,18 There was no serious complica- tion such as skin blistering or purpura as a consequence of wave reflection by HIFU.

In addition to the tightening effects of conventional regimens, the novel 6.0-mm transducer may further consolidate the reduction of the subcutaneous layer around SMF based on clinical observation. The mecha- nism for HIFU-based fat reduction has been demon- strated to involve both mechanical and thermal effects.19,20 At early time points, HIFU disrupts adipo- cytes mechanically by forming bubbles in the cells. Histologically, ultrasound destroys adipocytes selec- tively, leaving connective tissue, blood vessels, or nerves intact. Meanwhile, the controlled thermal effect of HIFU seems to provide precise and safe means for the removal of fatty tissues. The heat from the absorbed ultrasound energy triggers liquefaction and disruption of the membrane of adipocytes.21,22 The mechanical and thermal effects can occur together, and the mechanical activity enhances local heat deposition.23

In this study, instances of marginal mandibular nerve (MMN) paresis were not observed. The anatomical course of the MMN is variable and runs both inferior and superior to the mandibular border.24 Posterior to the antegonial notch, the MMN courses inferior to the mandible. Anterior to this bony landmark (at the anterior portion of the masseter muscle), the MMN courses superficially over the mandible to innervate the lip depressors.25 To prevent possible MMN injury, the authors applied the transducers beneath the line drawn 1.0 cm below the inferior mandibular border.

Topographical changes measured by 3D images establish changes in the surface areas over time, demonstrating the impact on the tissue that could potentially be related to reduced skin laxity.26–28 One important issue in cosmetic dermatology is the paucity of objective evaluation methods. Although craniofacial anthropometry and 2-dimensional photographs have been used, they have some limitations in clinical practicability and detection of volume changes.29 The introduction of 3D imaging software has advanced abilities to quantify both volume and surface area reduction in detail, allowing spatial analysis of numerous "facial contour rejuvenating" procedures. More quantitative measurements designed for tightening and reduction of the submental area with designated criteria based on a large clinical database would be required in the future studies.

There are some limitations in this study. First, all enrolled subjects were of identical ethnic origin. Second, further studies will be needed on the optimal parameters for each transducer and total number of treatment sessions. Third, the duration of follow-up observation was rather short. Although some of the patients have reported the long-term status, it would be more desirable to check the results for all patients 12 months after treatment. Finally, a comparative study with other devices or placebo will be useful because scoring may be favorably biased in single-arm studies. On the basis of these findings, the authors conclude

that the triple-layer HIFU regimen including a novel 6.0-mm transducer has benefits for the tightening and rejuvenation of the SMF area with reasonable safety profiles. Thus, this therapeutic regimen could be a viable option for SMF treatment in the Asian population.

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Quantified Facial Rejuvenation Utilizing High
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# Quantified Facial Rejuvenation Utilizing High Intense Focus Ultrasound with Multiple Penetrative Depths

Man-Lok Lio[1] | Chang-Cheng Chang[2-5] | Andy Deng-Chi Chuang[6] | Li-Cheng Tsai[7] | Chien-Chou Chen[8] | Taiwan

[1]Department of General Surgery, China Medical University Hospital, Taichung City, Taiwan; [2]Division of Plastic and Reconstructive Surgery, Department of Surgery, China Medical University Hospital, Taichung, Taiwan; [3]Department of Cosmeceutics and Graduate Institute of Cosmeceutics, China Medical University, Taichung, Taiwan; [4]School of Medicine, College of Medicine, China Medical University, Taichung, Taiwan; [5]Institute of Imaging and Biomedical Photonics, National Yang Ming Chiao Tung University, Tainan, Taiwan; [6]Department of Plastic and Reconstructive Surgery, Chang Gung Memorial Hospital at Keelung, Keelung, Taiwan; [7]Department of Dermatology, China Medical College Hospital, Taichung, Taiwan; [8]Department of Dermatology, Joe Chen Beauty Skin Clinic, Taichung City, Taiwan

**Correspondence**
Chang-Cheng Chang, China Medical University Hospital, No. 2, Yude Rd, North District, Taichung City 404, Taiwan,
Email changcc1975@gmail.com

**Background:** Multiple penetration depths of high-intensity focused ultrasound (HIFU) treatment for facial rejuvenation have not been quantified.
**Methods:** We enrolled 12 participants (n=24) to undergo one session of HIFU rejuvenation between January 1, 2019, and January 10, 2020. We used a 2-, 4.5-, and 6-mm focal depth transducer on the upper and middle face. We evaluated efficacy on days 60 and 90 by using our specific assessment system.
**Results:** The average eyebrow peak and pupil–eyebrow peak angles significantly increased by 2° ($p < 0.0005$) and decreased by 1° ($p < 0.0001$), respectively, at day 90. The shortened eyebrow–iris length indicated that the forehead tissues had lifted and moved medially to the central face. Supraorbital tissues were also vertically elevated, marked by the eyebrow–orbital ($p = 0.0016$) and vertical palpebral fissure lengths ($p = 0.0052$), which both exhibited a 0.8-cm elevation. For the midface, the increased canthus–oral–nasal angle ($p = 0.5881$) and decreased tragus–oral length ($p = 0.5881$) indicated that laxity had been corrected through lifted oral commissure, though the data were not statistically significant. No serious side effects were observed.
**Conclusion:** HIFU treatment with multiple depths quantitatively improved both upper-facial rejuvenation and midface rejuvenation after a single session.

**Keywords:** HIFU, high-intensity focused ultrasound, facial aging, facial periorbital rejuvenation, midface rejuvenation

## INTRODUCTION

Facial aging results in changes to the various anatomic layers of the skin, subcutaneous adipose tissue, muscles, retaining ligaments, and skeleton.[1] Facial rejuvenation tightens the affected facial connective tissues through collagen regeneration and recontouring. Surgical lifting and ablative resurfacing effectively treat moderate to severe laxity.[3] However, because of the relatively prevalent side effects and prolonged recovery time, nonablative skin rejuvenation has become a popular choice.[4] Modalities including laser-based treatment (eg NdYac or Alexandrite picosecond laser, and intense pulsed light) radiofrequency, and high-intensity focused ultrasound (HIFU) are used for skin rejuvenation through controlled thermal injury within the dermal region to trigger collagen remodeling; of these methods, HIFU is the only one that reaches the deep dermal and fibromuscular layer.[2,3]

HIFU eyebrow-lifting technology was approved by the Food and Drug Administration in 2009.[5] The acoustic energy generates heat ranging from 60° to 70 °C, targeting the deep dermis and superficial musculoaponeurotic system (SMAS), the so-called coagulation zone, which leads to collagen denature, new collagen synthesis, skin tightening, and elevation.[5,6] Anatomically, the thicknesses of facial skin layers vary slightly; thus, the depths of the targeted treatment

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layers must be adjusted accordingly. After adjustment of the deposited short pulse within 50 to 200 ms, the megahertz frequency, and the low energy within 0.5 to 1.5 J, HIFU can precisely target these programmed dermal depths with controlled source power for effective facial rejuvenation.[6,8]

Although many studies have evaluated the efficacy and safety of HIFU for use on the face, neck and other body regions,[2,6,7,9] the applied exposure parameters (source power, exposure area, and focal depth) have not been well described. Because programmed depth transducers are evolving, with new models being introduced on the market,[4] we assessed the efficacy of multiple depth transducers applied regionally to the upper and midface.

Our study introduced a single session of treatment for facial rejuvenation with multiple penetration depths (2, 4.5, and 6 mm) on the forehead, anterior and posterior temporal lobes, and zygomatic arches according to the depth of targeted tissue. We applied the treatment with ULTRAFORMER III (Classys, Seoul, Korea) novel transducers and evaluated its effectiveness by using our specific quantitative assessments based on anatomical landmarks.[22]

## MATERIALS AND METHODS

### Ethical Statement

The study was approved by the institutional review board of China Medical University Hospital in Taichung (Reference No CMUH109-REC1-137). All participants provided written informed consent for the trial, including consent for publication, and all procedures were conducted in accordance with the Declaration of Helsinki.

### Study Sample

Twelve participants between the ages of 20 and 60 years (2 men and 10 women; median age: 49.75 years) with Fitzpatrick skin type III–V were enrolled in our retrospective clinical review. All participants provided written informed consent for the trial. They received the HIFU treatment for facial rejuvenation between January 1, 2019, and January 10, 2020, and had not undergone any other aesthetic treatment. Individuals were excluded if they had undergone plastic surgery (eg, facelift, tissue augmentation, or blepharoplasty) before or between the aforementioned dates; treatments with fillers, or laser resurfacing; had scars, an infection, or a bleeding diathesis; or did not consent to the publication of their images.

### Procedures and Devices

During preparation, topical anesthetic (Sincaine cream 5%, with Lidocaine 25 mg, Prilocaine 25 mg per gm) was applied to the participants' forehead, temporal, and cheek regions for 20 minutes. One session of HIFU treatment was conducted, during which the ULTRAFORMER III targeted the forehead, temporal lobes, and zygomatic arches (see Supplementary Figure S1, figures, which outline the HIFU treatment lines, exposure parameters, and the expected consequential lifting effects) using the following three transducers:

- MF2; 5.5 MHz, 2-mm focal depth, applied at 0.3–0.4 J per line to the forehead.
- L4-4.5; 4 MHz, 4.5-mm focal depth, applied at 0.7 J per line to the anterior temporal lobes and zygomatic arches.
- W2-6.0; 2 MHz, 6-mm focal depth, applied at 1.0–1.2 J per line to the posterior temporal lobes.

Each treatment line was 25 mm, the standard interval between each thermal coagulation zone was 1.5 mm, and every treatment line contained 17 thermal coagulation zones. The entire procedure was conducted by the same physician, and transducers were applied perpendicularly, uniformly, and firmly to the skin surface. Treatment lines were adjacent and parallel to one another and approximately 3–5 mm apart. During treatment, 20, 10, 30, and 60 lines were applied to the zygomatic arches, anterior and posterior temporal lobes, and half of the forehead, respectively. The procedure was then repeated on the collateral side. In total, each participant received 240 exposure lines. One treatment session lasted 15–20 min. The total energy applied to the face was 138–162 J.

Standardized advanced imaging photographs (OBSERV A+, Myguard, Taoyuan, Taiwan) of the frontal (0°) were obtained pretreatment and on day 60 and 90 posttreatment. Participants were fixed in position under a standard OBSERV A+ lightening system. We assessed the efficacy of the treatment by comparing the designated angles and lengths before and after treatment (Figure 1).[22]





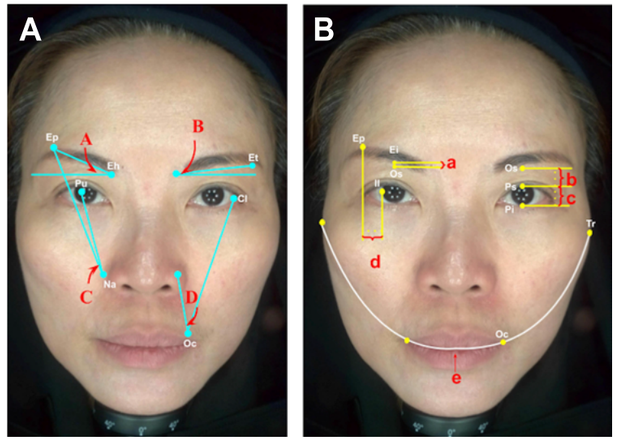


**Figure 1 (A)** Left, designed landmarks with four angular assessments. **(B)** Right, five linear assessments.
**Abbreviations:** Ep, eyebrow peak; Eh, eyebrow head; Pu, center of pupil; Na, lateral end of nasal ala; Oc, oral commissure; Et, eyebrow tail; Cl, lateral canthus; A, eyebrow peak angle; B, eyebrow tail angle; C, pupil–eyebrow peak angle; D, canthus–oral–nasal angle; Ep, eyebrow peak; Ei, inferior border of eyebrow; Os, superior orbital rim; Il, lateral limbus of iris; Ps, superior palpebral fissure; Pi, inferior palpebral fissure; Oc, oral commissure; Tr, tragus; a, eyebrow–orbital length; b, orbital–upper eyelid length; c, vertical palpebral fissure length; d, eyebrow–iris length; e, tragus–oral length.

### Efficacy Measurement: Objective Outcomes

Thirteen landmarks (see Supplementary Table S1, table, which explains the exact anatomies), four angular and five linear, were designed (Figure 1A and B). When eyebrow lifting is significantly improved, the eyebrow peak (E-peak) and eyebrow tail (E-tail) angles are increased. Elevated eyebrow peaks tend to move medially to the central side, resulting in a smaller pupil–eyebrow peak (P-E peak) angle (Table 1).

| Symbol | Length | Movement When Rejuvenation Present |
|---|---|---|
| a | Eyebrow-Orbital length | ↑ increased |
| b | Orbital-Upper Eyelid length | ↓ decreased |
| c | Vertical Palpebral Fissure length | ↑ increased |
| d | Eyebrow-Iris length | ↓ decreased |
| e | Tragus-Oral length | ↓ decreased |
| | **Angle** | |
| a | Eyebrow Peak angle | ↑ increased |
| b | Eyebrow Tail angle | ↑ increased |
| c | Pupil-Eyebrow Peak angle | ↓ decreased |
| d | Canthus-Oral-Nasal angle | ↑ increased |

**Table-1** Movement of the Linear and Angular Assessments When Rejuvenation Present After Treatment

**Abbreviations:** N, the sample size; SD, standard deviation; angles, degrees.

| n=24 | 0 Day | 60 Days | 90 Days |
|---|---|---|---|
| Eyebrow peak angle ± SD | 25.958° ± 4.554° | 26.750° ± 4.748° | 28.208° ± 3.923° |
| p value | / | 0.1322 | 0.0003 |
| Eyebrow tail angle ± SD | 3.417° ± 5.291° | 4.292° ± 4.573° | 4.250° ± 4.306° |
| p value | / | 0.1377 | 0.2011 |
| Pupil–eyebrow peak angle ± SD | 4.000° ± 2.414° | 3.917° ± 2.466° | 2.833° ± 2.057° |
| p value | / | 0.8024 | < 0.0001 |
| Canthus–oral–nasal angle ± SD | 29.625° ± 5.037° | 29.792° ± 4.644° | 29.958° ± 4.573° |
| p value | / | 0.7974 | 0.5881 |

**Table-2** Means of the Assessment Results for 12 Patients Along with the Angles, Standard Deviations, and p values < 0.05 Were Considered Statistically Significant

Three vertical lines and one horizontal line present the restoration of eyelid ptosis. When the superior orbital rim (Os) is set as an immobile landmark, the elevation of supraorbital tissues causes the eyebrow to lift, as indicated by a greater eyebrow–orbital (E-O) length. When the skin is tightened at the upper and lower eyelid, the length of the vertical palpebral fissure (VPF) increases. The flattening and tightening of the upper eyelid skin causes the orbital–upper eyelid length to decrease. According to the Westmore model, the ideal brow position is above the lateral limbus,[10] and when the eyebrow is lifted, the horizontal eyebrow–iris (E-I) length decreases (Table 1).

In terms of the midface, the distance between the bilateral tragi (Tr) passing through the oral commissure (Oc), so called the tragus–oral (T-O) length, should decrease if the sagging lower face is restored by rejuvenative procedures. These measurements were collected in the same manner collaterally.

### Statistical Analyses

GraphPad Prism 6 software[26] was used for statistical analyses. Statistical comparisons before and after the treatment were performed using paired t-tests. Data were presented as the mean ± standard deviation, and p values < 0.05 were considered statistically significant.

## RESULTS

The mean values of the eyebrow-peak and E-tail angles were increased at days 60 and 90 (Table 2) (see Supplementary Figure S2, figures, which present the results of the angular assessment in a boxplot). The E-peak angle increased from 25.958° ± 4.554° on day 0 to 28.208° ± 3.9232° at the day 90 follow-up, constituting a statistically significant improvement of 2° (p = 0.0003), approximately. The mean of the E-tail angle on day 90 was 4.250° ± 4.306°, which also constitutes an increase of approximately 1° compared with baseline, though the result was not statistically significant (p = 0.2011). The P-E peak angle was 4.000° ± 2.414° at baseline. The lifted and contracted supraorbital and forehead tissues caused the eyebrow peak to move medially to the central side, resulting in a significant, approximate 1° decrease in P-E peak angle on day 90 follow-up (2.833° ± 2.057°, p < 0.0001). Regarding the periorbital region, the means of both the E-O and VPF lengths were significantly higher at days 60 and 90, with an approximate 0.8 mm improvement (p = 0.0016; p = 0.0052, respectively) (Table 3) (see Supplementary Figure S3, figures, which present the results of the linear assessment in a boxplot).

The mean of the orbital–upper eyelid length decreased from 7.204 ± 2.208 mm to 6.588 ± 1.909 mm at day 90 (p = 0.0352). All data were statistically significant. According to horizontal linear measurements, the E-I length was shorter at day 90 (6.633 ± 2.463 mm) than at baseline (6.813± 2.663 mm), though the difference was not statistically significant (p = 0.5440).





**Abbreviations: N, the sample size, SD, standard deviation, mm, millimeter.**

| n=24 | 0 Day | 60 Days | 90 Days |
|---|---|---|---|
| Eyebrow–orbital length (mm) ± SD | 3.100 ± 1.184 | 3.600 ± 1.304 | 3.991 ± 1.409 |
| p value | / | 0.0126 | 0.0016 |
| Orbital–upper eyelid length (mm) ± SD | 7.204 ± 2.208 | 6.883 ± 1.848 | 6.588 ± 1.909 |
| p value | / | 0.2431 | 0.0352 |
| Vertical palpebral fissure length (mm) ± SD | 11.163 ± 1.157 | 11.758 ± 1.775 | 11.979 ± 1.187 |
| p value | / | 0.1034 | 0.0052 |
| ebrow–Iris length (mm) ± SD | 6.813± 2.663 | 7.250 ± 2.933 | 6.633 ± 2.436 |
| p value | / | 0.1411 | 0.5440 |
| **n=12** | **0 Day** | **60 Days** | **90 Days** |
| Tragus–oral length (mm) ± SD | 169.893 ± 26.617 | 171.400 ± 27.531 | 168.852 ± 25.354 |
| p value | / | 0.4477 | 0.4943 |

**Table-3** Means of the Assessment Results for 12 Patients Along with the Lines, Standard Deviations, and p values < 0.05 Were Considered Statistically Significant

For the midface, the average canthus–oral–nasal (C-O-N) angle was 29.625° ± 5.037° at baseline and exhibited a 0.3° increase to 29.958° ± 4.573° at day 90. The average tragus–oral (T-O) length decreased from 169.893 ± 26.617 mm at baseline to 168.852 ± 25.354 mm at day 90, representing a decrease of approximately 1 mm (Table 3). The data indicate that laxity of the midface was corrected and oral commissure was lifted, though not to a statistically significant level (p = 0.5881, p = 0.4943).

### Side Effects

Pain and mild erythema in the treatment area were noted for 6 patients during treatment. These effects were soon resolved after treatment and did not last longer than 2 days. No serious side effects were reported during the study.

## DISCUSSION

HIFU treatment for facial rejuvenation is in high demand because it is minimally invasive, does not cause any epidermal damage, and can reach targeted skin layers at various depths with penetrating probes. Our current understanding of aging suggests that facial aging is not simply a result of the atrophy of subcutaneous fat but rather fatty hypertrophy, especially in the infraorbital, lateral temporal cheek, and submental region.[18,21] In 2007, Gliklich et al and White et al studied the propagation of HIFU energy in cadaveric tissues to demonstrate that the formation of thermal injury zones, mainly in the SMAS layer, leads to thermal collagen denaturation and subsequent synthesis.[12,17] Other in vivo studies have reported that collagen and elastic fibers develop after HIFU treatment primarily in the reticular and deep dermis.[8,11,16,17] At a deeper tissue matrix, HIFU transducers thermally modify collagen and ablate adipocytes, thereby causing shrinkage and collagen remodeling within the tissue matrix and eventually reenforcing the attenuated ligaments and muscles. The depths of facial retaining ligaments and subdermal fascia vary because the thickness of anatomical components, such as superficial fat compartments and dermal tissue, tend to increase with age.[16,17,20,21] Hence, the application of more than one transducer in HIFU treatment was vital in our study. To our knowledge, a 1.5-mm transducer is commonly used for superficial dermis, a 3-mm transducer is used for deeper dermis, and a 4.5-mm transducer targets the SMAS layers.[4] Transducers sized 6 mm and above are often used in body recontouring for areas such as the abdomen and thighs.[8,9]

In our study, we applied a novel 2-mm transducer as a superficial transducer on the forehead (generated energy was 36–48 J). After one session of treatment, significant eyebrow lifting was observed at day 90 of follow-up. Additionally, the forehead tissue had contracted and moved supraorbital tissue medially to the central face. The lifting of the periorbital

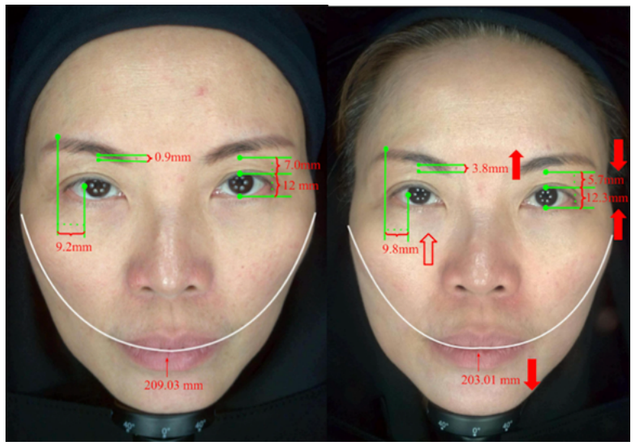


**Figure 2** (Left) Pretreatment (day 0) and (Right) posttreatment (days 90) comparison using our designed angles and lengths system. Upward red arrows mean the data was increased posttreatment (days 90) and vice versa. Solid arrows mean rejuvenation was obtained and hollow arrow means no rejuvenation posttreatment (days 90).
Standardized photographs were obtained with OBSERV A+.

tissues was evidenced by an increase in mean E-O and VPF lengths, which indicated that the supraorbital ligamentous attachments had also thermally contracted and lifted (Figures 2A and B).

Our study is the first to report the use of a 6-mm deep transducer in facial rejuvenation, especially on the hair-bearing region of the temporal area, which is typically used on other body regions.[12,14] Kwon et al proved a 6-mm transducer has benefits for tightening and rejuvenation of the area with unwanted fat.[23] Because both the skin and fat of the lateral temporal and cheek regions are relatively thick, 4.5- and 6-mm transducers were employed to target the SMAS or deeper layers. We applied the MF6 (6 mm, 2 MHz, 1.0–1.2 J) to the posterior temporal lobes (generated energy was 60–72 J), extended the treatment site further to the hair-bearing region and scalp, in order to target the temporal fat pad in between the superficial and deep layers of the deep temporal fascia, which create a resonance between these two temporal fascia layers. For the concern of hair root injury, Jimenez et al[24] studied the morphometric analysis of scalp hair and stated the mean length of human scalp hair follicle is 4.16mm, the data of Vogt et al[25] reviewed the mean length of hair follicle is 3.86 mm; our applied 6-mm transducer targeted even deeper layers of the scalp, and no reports of epilation was noted in the post-treatment visits.

The increased E-tail angle and decreased E-I length indicated that the entire fascia of the temporal compartment contracted and subsequently lifted. Rejuvenation was also extended to the midface, as evidenced by the increase in the C-O-N angle and decrease in T-O length; therefore, laxity of the midface was restored and the oral commissure was lifted.

Some authors compared the aesthetic improvements of HIFU at two focal depths with improvements at a single focal depth. Baumann et al concluded that treatment with two focal depths is superior that with a single focal depth on the neck and lower face.[13] However, research demonstrating the efficacy of multiple transducers on more than two regional uses is limited. The application of HIFU transducers to the upper to midface is also limited to only one or two focal depths.[14] Suh et al[11] reported clinical and histologic improvements in a study on 22 Korean participants after treatment with a single HIFU transducer on the forehead (3 mm, 0.3–0.35 J), temples (3 mm, 0.35 J), and malar areas. Park et al[5] recorded a significant tightening of infraorbital laxity in seven patients treated with 1.5-mm (0.2 J) and 3-mm (0.45 J) focal depth transducers (with a total of 30 treatment lines). Recently, Kwon et al23 studied the efficacy of multiple transducers (3, 4.5 and 6.5 mm) applied on submental for reduction of unwanted submental fat. Our study design integrated the application of more transducers (2, 4.5 and 6 mm) on a single session of treatment. We validated the effectiveness quantitatively by using multiple penetration depths and transducers with deep focal depths for upper-facial and midfacial rejuvenation.

Thus far, no consensus has been reached on the ideal objective measurements for aesthetics. Traditional assessment tools, such as the Global Aesthetic Improvement Scale (GAIS) and wrinkle severity rating scale (WSRS), completed by both patients and physicians before and after treatment, are commonly used to assess HIFU treatment,14 but these 5-point scales cannot accurately represent treatment efficacy.14,15 Alam et al19 also evaluated the outcomes of HIFU treatment in eyebrow lifting by using fixed landmarks but measuring only linear changes and not employing anatomical landmarks on the lower face. In order to determine the cosmetic effects and quantity of skin lifting, our study employed a standard measurement of 13 facial landmarks, measuring the changes to four angles and five lines, according to which the efficacy of facial lifting was determined objectively.

This study has some limitations. First, we did not have a control group and it was almost impossible to hold a prospective, randomized clinical trial based on the personal heterogeneities, such as the degree of aging among people. Second, we did not compare the efficacy with a single transducer and the sample size was small and only analyzed the skin type of Asian, it is hard to determine which age group gave the best results. Third, the effects of repeated sessions were undetermined. Long-term adverse effects that may have occurred after the 90 days follow-up period were still not observed.

## Conclusion

We assessed and quantified the efficacy of using multiple penetration depth transducers in HIFU treatment for facial rejuvenation. In our study, the results were favorable after one treatment session, and the side effects were transient and minimal. We confirmed that facial rejuvenation at the upper face and midface can be achieved through the use of transducers with multiple penetration depths (2, 4.5, and 6 mm). The variety of penetrative depths and sessions can potentially achieve even more effective results.

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## Disclosure

The authors report no conflicts of interest in this work.

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# A new treatment protocol of microfocused ultrasound for lower eyelid fat bulging

Hye Chan Jeon[a] | Do-Yeop Kim[b*] | Seon-Pil Jin[c] | Dong Hun Lee[b]

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# A new treatment protocol of microfocused ultrasound for lower eyelid fat bulging

Hye Chan Jeon[a] | Do-Yeop Kim[b*] | Seon-Pil Jin[c] | Dong Hun Lee[b] | South Korea

[a]The Seoul Dermatology Clinic, Seoul, Korea; [b]Department of Dermatology, Seoul National University College of Medicine, Seoul, Korea; [c]Dermatology Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, USA

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## ABSTRACT

**Background:** Microfocused ultrasound (MFU) causes tissue tightening by producing thermal injury zones and is used to treat various age-related changes including lower eyelid fat bulging.

**Objective:** To investigate the efficacy of a new treatment protocol of MFU for lower eyelid fat bulging.

**Methods and materials:** We reviewed the medical records of all patients who began MFU for lower eyelid fat bulging from March 2017 to September 2018. MFU was performed in two steps to tighten the lower eyelid dermis and orbital septum. Data on age, sex, bulging severity, and the number of treatment sessions were obtained. Associations of these variables with treatment response were determined through an ordinal logistic regression analysis.

**Results:** Among 191 enrolled patients, 119 (62.3%) and 47 (24.6%) achieved fair and good responses, respectively. In the multivariable analysis, multiple treatment sessions (odds ratio (OR) 6.618; 95% confidence interval (CI) 3.242–13.513; p<.001), moderate bulging (OR 4.328; 95% CI 1.755–10.671; p¼.001), and severe bulging (OR 7.570; 95% CI 2.537–22.585; p<.001) were associated with greater treatment response. There were no serious adverse events.

**Conclusions:** The new treatment protocol of MFU is an effective and safe strategy for lower eyelid fat bulging.

## INTRODUCTION

As aging progresses, lower eyelid fat bulging becomes prominent because of age-related changes in the soft tissue and bony orbit (1). One of its major causes is the loosening of the orbital septum that supports orbital fat. Lower blepharoplasty can be performed for correction, but problems such as scarring, long recovery time, and overcorrection might occur. Thus, effective but non-to-minimal invasive methods for managing lower eyelid fat bulging have been required. Recently, non-surgical treatments such as ablative and non-ablative fractional laser, radiofrequency, and microfocused ultrasound (MFU) have been used (2–5).

MFU produces discrete thermal injury zones to targeted areas, which results in shrinkage and tissue tightening (6). Moreover, it can raise the temperature of the targeted adipose tissue while sparing the surrounding tissue, and no damage to intervening nerves or arterioles was observed within the path of the ultrasound pulse (7). Given that the power density of the converging ultrasound beam is much lower as it passes through the path above the target point (8), MFU is believed to be safe when used off-label for orbital fat treatment, and no serious adverse events have been reported in human eyelid studies (5,9).

However, when the orbital septum is deeply located, energy delivery to the orbital septum is limited in the conventional protocol (5,9). Also, the shape and location of orbital fat of most patients are not consistent in the supine position compared to the sitting position. In this study, we reported the efficacy of a new two-step protocol of MFU that tightens both lower eyelid dermis and orbital septum for correcting lower eyelid fat bulging.

## METHODS

### Study population and variables

We reviewed the medical records of patients with lower eyelid fat bulging who started MFU at the The Seoul Dermatology Clinic from March 2017 to September

**CONTACT** Dong Hun Lee ivymed27@snu.ac.kr Department of Dermatology, Seoul National University College of Medicine, 103 Daehak-ro, Jongno-gu, Seoul 03080, Korea; Seon-Pil Jin seon-pil.jin@nih.gov Dermatology Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, USA Both authors contributed equally to this work.

2018. All patients were followed up until we confirmed that no further treatment is needed, until they were lost to follow-up, or until October 15 2018 (date of scheduled data extraction), whichever arrived earlier. Patients who were lost to follow-up after the first treatment were excluded. Age, sex, and the number of treatment sessions were obtained from the medical records.

**Evaluating bulging severity and treatment results**

High-resolution digital photographs taken with a Canon EOS D30 camera (en face; Canon, Lake Success, NY) were used to assess bulging severity and treatment response. Baseline bulging severity was scored from 1 to 5 using photographs taken before initial treatment, with 1 indicating mild bulging and 5 indicating most severe bulging. The severity scores were converted into a single ordinal variable by summing the number of individual scores by three independent dermatologists in the mild (3–6), moderate (7–10), and severe (11–15) categories.

Treatment response was graded as follows by comparing photographs taken before the initial treatment and at the last visit: grade 0, no improvement; grade 1, <20%; grade 2, 20–39%; grade 3, 40–59%; grade 4, 60–79%; and grade 5, 80–100%. We also collapsed treatment response grades into a single ordinal variable by summing the number of individual grades by three dermatologists in the minimal (0–2), fair (3–5), and good (6 or more) responses. There were no missing data in this study because we had started to take photographs of patients with lower eyelid fat bulging at every visit as of January 2017.

The study protocol was approved by the Institutional Review Board of Korean National Institute for Bioethics Policy (P01- 201903-21-001), and the requirement for obtaining informed consent was waived.

**Intervention**

We used the ULTRAFORMER III, SHURINK MFU device (Classys Inc., Seoul, Korea) with three different transducers. The EMLA cream (lidocaine 2.5% and prilocaine 2.5%; Astra Pharmaceutical Products Inc., Westborough, MA) was applied to the treatment site 60 min before treatment. After the EMLA cream was wiped off, an ultrasound gel was applied to the skin.

In the first step, MFU was performed on the patients in the supine position using the L7-1.5 transducer (7 MHz, 1.5-mm focal depth) and either the L7-3.0 (7 MHz, 3.0-mm focal depth) or the L4-4.5 transducer (4 MHz, 4.5-mm focal depth) to tighten the lower eyelid dermis and orbital septum. Either the L7-3.0 or the L4-4.5 transducer was used depending on the depth of the orbital septum, which was measured before treatment using a handheld ultrasound device (UProbe-L5NC, Sonostar Technology Co., Guangzhou, China). To ensure that the orbital septum could be targeted by each shot, we applied proper pressure toward the infraorbital margin with the transducer during the procedure.

Moreover, in the second step, L7-3.0 and L4-4.5 transducers were used in patients in the sitting position to tighten the orbital septum. While the transducer was being used, patients were instructed to open their eyes and look upwards.

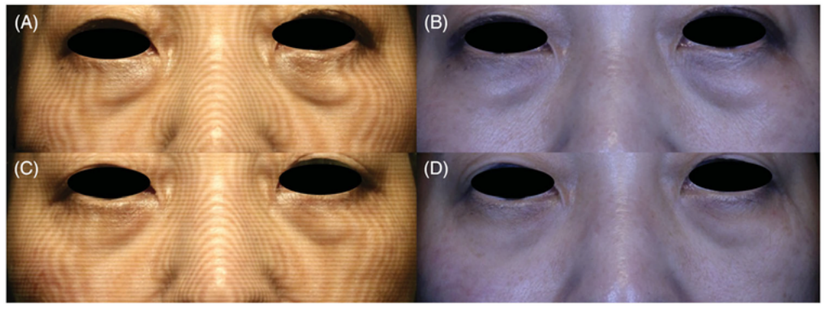


**Figure 1** Demographic and Baseline Characteristics





The energy per ultrasound pulse used at the first and second steps ranged from 0.10 to 0.20 J and from 0.3 to 0.5 J, respectively. The 25-mm-long exposure lines of ultrasound pulses were delivered parallel to one another with 3-5-mm spacing. Treatment lines were delivered to the skin located 2mm below the lower eyelid margin to the inferior orbital rim, parallel to the lower eyelid margin. Patients receiving multiple sessions were treated at 3-week intervals.

**F-RAY**

To attempt a more precise evaluation of bulging severity and treatment response, additional photographs were taken using the F-RAY (Beyoung Co., Seoul, Korea). This device creates contour lines using the moir e phenomenon; thus, it is expected to enable more sensitive volume assessment (Figure 1). Three dermatologists evaluated baseline bulging severity and treatment response with photographs taken with F-RAY in the same way as when evaluating with conventional digital camera photographs.

**Statistical analysis**

Ordinal logistic regression analyses were used to evaluate associations between predictive factors and treatment response.

Predictive factors showing univariable associations with treatment

response ($p<.20$) were included in a multivariable ordinal logistic regression model.

Interrater reliability for bulging severity and treatment response scores was assessed using Spearman's correlation. Differences in the treatment response evaluation (conventional digital camera vs. F-RAY) were analyzed with the exact McNemar–Bowker test. All analyses were performed using SPSS statistics software, version 20.0 (SPSS Inc., Chicago, IL). All statistical tests were two-sided and a p value<.05 was considered statistically significant.

## RESULTS

**Patients' characteristics and overall treatment response**

Detailed demographic and clinical characteristics of the patients are presented in Table 1. A total of 191 patients with lower eyelid fat bulging were identified and treated with MFU; of these, 162 (84.8%) were female. Patients' mean age at the time of presentation was 45 (range 20–73) years. The median treatment number per patient was 1 (interquartile range (IQR) 1–2).

The median bulging severity score was 9.0 (IQR 7.0-10.0), and median treatment response score was 4.0 (IQR 3.0–5.0). Overall, when evaluated by photographs taken with the conventional digital camera, 25 (13.1%) have had a minimal response, 119 (62.3%) a fair response, and 47 (24.6%) a good response (Figure 2). The proportion of patients with good response tended to increase with the number of treatments (Figure 3).

| Variable | All patients (n¼191) |
|---|---|
| Age, mean (range), years | 45.3 (20.0–73.0) |
| Sex, n (%) | |
| Male | 29(15.2) |
| Female | 162 (84.8 |
| Number of treatment, median (IQR) | 1.0 (1.0–2.0) |
| Bulging severity scorea, median (IQR) | 9.0 (7.0–10.0) |
| Treatment response scoreb, median (IQR) | 4.0 (3.0–5.0) |

IQR: interquartile range.
[a]Mild (3–6), moderate (7–10), severe ( 11).
[b]Minimal (0–2), fair (3–5), good ( 6).

**Table 1** Demographic and clinical characteristics of patients.

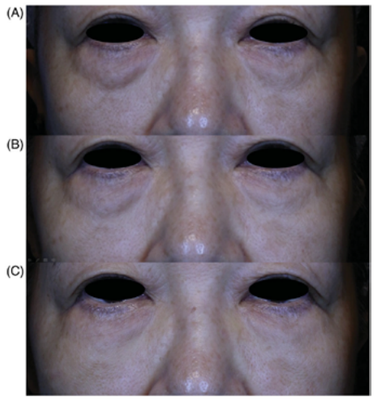


**Figure 2** Preoperative and postoperative photographs using a conventional digital camera in a patient with a good response. Compared with pretreatment (A), photographs after the third treatment (B) and the seventh treatment (C) show gradual improvement.

### Association between predictive factors and treatment response

As shown in Table 2, the univariable ordinal logistic regression analysis revealed multiple treatment sessions, and more severe lesions were associated with greater treatment response (Table 2). There were no significant differences in the treatment response according to age and sex.

In the multivariable ordinal logistic regression analysis, two variables (treatment number and bulging severity) remained significantly associated with treatment response (Table 2). Multiple treatment sessions were significantly associated with greater treatment response (odds ratio (OR), 6.618; 95% confidence interval (CI) 3.242–13.513; p<.001). Additionally, patients with moderate or severe lesions showed greater treatment response than patients with mild lesions (OR 4.328; 95% CI 1.755–10.671; p¼.001, and OR 7.570; 95% CI 2.537–22.585; p<.001, respectively) (Table 2).

### Comparison of evaluation by digital camera and F-RAY

Average interrater reliability (Spearman) of bulging severity score and treatment response score evaluated by the conventional digital camera was 0.40 and 0.33, respectively. When evaluating using F-RAY, the average interrater reliability increased to 0.52 (p¼.139) and 0.39 (p¼.504), respectively, which was not significantly different. Figure 4 compares the treatment responses evaluated by a conventional digital camera and FRAY. There were significantly more fair and good responses evaluated by the F-RAY than by the conventional digital camera (p¼ .003). This suggests that a more sensitive and reproducible evaluation has been done when evaluating with F-RAY.

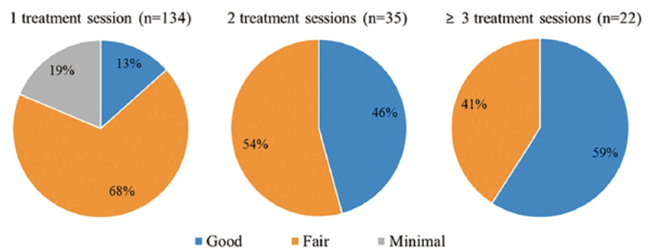


**Figure 3** Frequency of treatment response depending on the number of treatment sessions.





| | Univariable analysis | | | | | Multivariable analysis | |
|---|---|---|---|---|---|---|---|
| Variable | Minimal response (n¼25) | Fair response (n¼119) | Good response (n¼47) | OR (95% CI) | p Value | OR (95% CI) | p Value |
| Age, years, median (IQR) | 44.0 (39.0–48.0) | 47.0 (36.0–53.0) | 49.0 (39.0–54.0) | 1.011 (0.984–1.039) | .418 | - | |
| Sex, n (%) | | | | | | - | |
| Female | 22 (88.0) | 100 (84.0) | 40 (85.1) | Reference | | - | |
| Male | 3 (12.0) | 19 (16.0) | 7 (14.9) | 1.081 (0.489–2.390) | .848 | | |
| Treatment number, n (%) | | | | | | | |
| 1 | 25 (100.0) | 91 (76.5) | 18 (38.3) | Reference | | Reference | |
| ≥2 | 0 (0) | 28 (23.5) | 29 (61.7) | 7.720 (3.827–15.571) | <.001 | 6.618 (3.242–13.513) | <.001 |
| Bulging severity, n (%) | | | | | | | |
| Mild | 9 (36.0) | 18 (15.1) | 0 (0) | Reference | | Reference | |
| Moderate | 15 (60.0) | 77 (64.7) | 32 (68.1) | 5.266 (2.160–12.840) | <.001 | 4.328 (1.755–10.671) | .001 |
| Severe | 1 (4.0) | 24 (20.2) | 15 (31.9) | 10.711 (3.736–30.734) | <.001 | 7.570 (2.537–22.585) | <.001 |
| CI: confidence interval; IQR: interquartile range; OR: odds ratio. | | | | | | | |

**Table 2** Univariable and multivariable analyses of treatment response to MFU in lower eyelid laxity (n¼191).

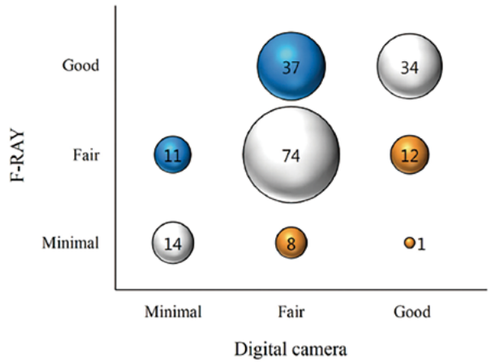


**Figure 4** Comparison of treatment responses evaluated by conventional digital camera and F-RAY (n¼191). Significant asymmetry (p¼ .003, Bowker test), i.e. significantly more fair and good responses evaluated by the F-RAY than by the conventional digital camera.

### Safety assessment

The most common adverse events were pain and swelling (reported by approximately half of the patients), which were mild in severity. Other adverse events observed were bruising (reported by five patients), nodules (reported by two patients), ectropion (reported by one patient), and unilateral dacryorrhea (reported by one patient). All adverse effects were mild and resolved within 2 weeks. No serious adverse events were reported.

## Discussion

This study investigated the efficacy and prognostic factors of a new two-step MFU protocol to tighten the lower eyelid dermis and orbital septum in patients with lower eyelid fat bulging. More than 80% of patients showed a fair or good response after undergoing the treatment with the new MFU protocol. Moreover, we showed that the clinical factors associated with the greater treatment response were multiple treatment sessions and moderate or severe bulging. Age and sex were not associated with the treatment response. In the first step, we employed a relatively lower energy (0.1–0.2 J) than 0.2–0.45 J from conventional protocols to reduce the risk of untoward side effects, and added the second step using a higher energy (0.3–0.5 J) with a 3.0 mm- or 4.5 mm-focal depth probe for effectively targeting the orbital septum as well as tightening the lower eyelid dermis. Also, looking upwards in the sitting position allows the orbital fat to bulge out so that physicians can treat it more precisely. In studies using conventional protocols of MFU for lower eyelid fat bulging, Suh et al. (9) reported that 86.7% of patients were considered to have much improved or improved lower eyelid, and Pak et al. (5) reported an average improvement score of 3.45 and 3.25 on a scale of 0 (no involvement) to 4 (severe). It is difficult to compare the efficacy of the conventional and new treatment protocols directly because the evaluation was carried out 6 months after the single treatment session in previous studies, and the grading scale was different.

When treating the lower eyelid fat bulging with MFU, careful treatment is needed because the therapeutic response varies greatly depending on how precise the

orbital septum is targeted (5). First, the target depth assessment through diagnostic ultrasound should be preceded to select probes for the appropriate treatment depth. During the procedure, the orbital septum becomes shallower as pressure increases; thus, proper pressure should be applied to adjust the target depth. Moreover, the probe should be placed parallel to the lower eyelid margin. If the probe is placed perpendicular to the lower eyelid margin, as Pak et al. (5) reported, the orbital septum would become deeper. To keep the depth change constant during the procedure on the orbital septum, it would be better to target the part that originates from the orbital rim.

It is also important to stay on the bone when treating the periorbital area, because the ultrasound waves will bypass any protective eye shield and can cause corneal damage (10,11). If the MFU is performed toward the inferior orbital rim, eye damage can be avoided without the need for an eye shield. In the second step, corneal damage was prevented by instructing patients to look upwards. Although one additional treatment step has been added, it was well tolerated with an adverse event profile similar to those in previous studies. Meanwhile, high-intensity focused ultrasound in bone metastasis is known to increase skeletal remodeling (12), and a similar mechanism may contribute to improving lower eyelid fat bulging through the 'hammock effect' (1).

Diagnostic ultrasound can also be used to distinguish other conditions that can be confused with fat bulging (13). In dark circles with which the causes other than fat bulging are predominant, the effect of MFU is reduced and it may be better to perform other treatments. For example, treatment with a polynucleotide or hyaluronic acid can yield satisfactory results in dark circles due to the thin, translucent skin (14).

We found that the number of treatment sessions was associated with treatment response. Improvement can be more pronounced with a longer observation period because the lipolysis
and tightening process can last more than three months after a single session of MFU (15). However, since the proliferative phase lasts for approximately 21 days in the wound healing process (16), frequent treatments at 3-week intervals may lead to a rapid improvement.

In this study, more severe bulging led to better clinical outcomes. Although the severe group tended to receive more treatment sessions, the significance was still maintained in the multivariable analysis. In general, mild-to-moderate laxity is considered to be an ideal indication for MFU (10,17), but the satisfactory outcome can also be expected in severe cases.

We found that age was not associated with treatment response to MFU. This is consistent with two retrospective chart reviews showing that age was not associated with patient satisfaction after MFU (18,19). Although previous studies have reported that younger patients are more likely to have a good outcome, no statistical analysis was performed in these studies (17,20).

The evaluation using F-RAY was more sensitive, because the fluctuations of the skin surface can be evaluated more delicately with the aid of contour lines (21). In addition, this device minimizes ambient light interference by using a blackout curtain and takes standardized photographs at a consistent angle by using cephalostats for the forehead and chin. It is also noninvasive; thus, it will be useful for the precise evaluation without any inconvenience.

Our study had several limitations. Similar to other retrospective chart review studies, it is possible that there were unmeasured confounding factors, such as patient compliance. In addition, extent of fat bulging was not quantitatively measured. However, for more reliable results, we combined the scores of three independent dermatologists and also evaluated using F-RAY.

In conclusion, our results suggest that the new treatment protocol of MFU is effective and safe for lower eyelid fat bulging regardless of age and sex. Clinicians could consider additional MFU sessions if the improvement is not apparent after the first treatment.

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## DISCLOSURE STATEMENT

The authors report no conflict of interest.

## ORCID

Do-Yeop Kim http://orcid.org/0000-0002-7500-5055



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# The Efficacy of High-Intensity Focused Ultrasound Treatment for Sagging Upper and Lower Eyelids

Yousun Hwang, MD[1] I Kyu-Ho Yi, MD, PhD[2]

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The AESTHETICS

# The Efficacy of High-Intensity Focused Ultrasound Treatment for Sagging Upper and Lower Eyelids

Yousun Hwang, MD[1] I Kyu-Ho Yi, MD, PhD[2] I South Korea

[1]Haedrin Clinic, Center for Aesthetic Medicine, Seoul, Korea
[2]Wonju Public Health Center, Wonju, Korea

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Correspondence
Yousun Hwang
Haedrin Clinic, Center for Aesthetic Medicine, Seoul 03779, Korea
E-mail: clarasong4528@gmail.com
https://orcid.org/0000-0001-5688-1992

**Background and Objectives:** Eyelid sagging is a common complaint in aging patients. Although various attempts have been made to treat this condition, obtaining satisfactory results in patients without causing adverse effects has been challenging. The study
demonstrated that high-intensity focused ultrasound (HIFU) can be a valuable tool for the treatment of eyelid sagging.
**Materials and Methods**: Twenty Korean women aged 35 to 57 years with mild to moderate upper and lower eyelid sagging were enrolled. The periocular area of the participants was treated with a 2.0-mm, 4-MHz HIFU probe. Photographs were taken before and 12 weeks after the treatment. Two clinicians who were blinded to participant recruitment evaluated improvements. Perceived improvement was rated by both patients and clinicians on a 4-point scale. The eyelid length was measured and compared before and after treatment.
**Results:** The results showed that 17 patients (85%) experienced some clinical improvement. In 15 of the 20 cases, clinicians were able to detect improvement. In addition, the mean eyelid length was reduced 12 weeks after treatment, indicating that the treatment is a potentially effective method for successfully treating eyelid aging.
**Conclusion:** HIFU is a useful method for improving upper eyelid sagging.

**Key words:** High intensity focused ultrasound, Eyelid sagging, Skin lifting

## INTRODUCTION

The periocular region shows the most prominent and early facial signs of aging [1]. The eyelid is one of the thinnest areas of the face [2], and aging eyelids show a decrease in elastic fibers with ultrastructural abnormalities and overexpression of elastin-degrading enzymes, which can result in prominent sagging [3]. As cutaneous changes and subsequent skin sagging can cause significant distress [4], the clinical management of this problem can enhance emotional well-being. Various surgical procedures, such as upper eyelid blepharoplasty, eyelid reconstruction, and eyebrow lifting, have been used widely to address these issues. However, because of the invasive nature of the surgery and its possible side effects, the demand for non-invasive treatment options is high [5]. Therefore, diverse non-invasive procedures have been introduced to restore youthful facial appearance [6]. In addition to botulinum toxin, fillers, radiofrequency treatment, and lasers [7], high-intensity focused ultrasound (HIFU) is a popular treatment modality with the treatment goal of rejuvenating and tightening the skin [8]. Ultrasound energy penetrates the subcutaneous tissue to several millimeters in depth, producing thermal coagulation points that cause collagen fiber synthesis in the superficial muscular aponeurotic system and platysma [9]. A meta-analysis of the efficacy of HIFU for the face and neck showed moderate improvement in objective and subjective measurement scores [10]. However, despite the positive results of HIFU treatment for skin rejuvenation and face and neck tightening [8,11], its effectiveness on the eyelids has not yet been established. We hypothesized that HIFU may not only be a good treatment for tightening the mid and lower facial skin but also for tightening the eyelids. Here, we report the effectiveness of HIFU treatment for the eyelids and how we were able to safely treat this part of the eye.

## MATERIALS AND METHODS

### 1. Patients

Twenty Korean women aged 30-60 years (Fitzpatrick skin type III and type IV) who complained of mild to moderate skin laxity of the eyelids were enrolled in the study. The exclusion criteria included active infection or skin diseases in the periocular area, pregnancy, history of keloidal scarring, and history of anti-aging procedures within 12 months prior to the study. All the patients provided informed consent at the time of enrollment.

### 2. Treatment Protocol

For each patient, a topical anesthetic cream (5% lidocaine- prilocaine) was applied to the periocular area, including the upper and lower eyelids and crow's feet area, for 40 min before the procedure after their faces had been cleansed. One HIFU device (Ultraformer III, Classys Inc.) was used for treatment because of its 2.0-mm probe that was specially designed to treat the periocular area. The energy parameter for the treatment was set at 0.3 J. For every patient, 40 treatments shot were applied to the upper eyelids, lower eyelids, and crow's feet (20 shots on each side). Therefore, a patient received 120 shots in total. During the entire procedure, the probe was firmly positioned perpendicular to the skin surface with constant movement to ensure appropriate energy delivery into the tissue. Corneal protectors were applied to each patient's eyes to ensure safety.

### 3. Outcome evaluation

Participants were evaluated on the day of treatment and 12 weeks after treatment. Digital photographs were obtained under similar lighting conditions. Photographs of the frontal view of the face as well as of the face at an angle of 45° on each side were obtained. The photographs obtained before and after the 12 weeks treatment were assessed by two clinicians who were blinded, and they were asked to choose a post-treatment image to assess the overall improvement, tightening of sagging eyelids, and improvement of crow's feet using a 4-point scale ranging from 1 to 4 (1 = little or no improvement [< 25%], 2 = mild improvement [26%-50%], 3 = moderate improvement [51%-75%], and 4 = marked improvement [76%-100%]). Each patient was also asked to rate their perception of the overall improvement in the periocular area, tightening of sagging eyelids, and improvement of crow's feet using the same scale. Any side effects or discomfort during treatment, after treatment, and at the follow-up visit were recorded.

In addition, to objectively assess improvements, a perpendicular line was drawn which passed through the midline between the medial and lateral canthus and measured the distance between the point at which the line met the eyebrow and the point at which the line met the upper rim of the eye. The average of the right and left side distances was calculated for each patient as the average lid length (ALL). ALL was calculated immediately before treatment and 12 weeks after treatment. After recording all the ALLs of the 20 participants, the mean ALL before and after the treatment was each calculated to determine the significant difference the two measurements.

## RESULTS

All the 20 patients (all female) completed the treatment program and were available for the follow-up assessment after 12 weeks.

Their ages ranged from 35 to 57 years (mean: 46.00 ± 7.41 years); 15 patients had Fitzpatrick skin type III, and 5 had Fitrzpatrick type IV.

Seventeen patients reported a degree of overall improvement in the periocular area 12 weeks after the treatment. Their average 4-point scale score for the overall improvement was 2.35 (mean: 2.35 ± 0.81). The average eyelid skin tightening score was 2.30 (mean: 2.30 ± 0.86). The average crow's feet score was 2.25 (mean: 2.25 ± 0.97). The mean VAS score was 4.45 ± 1.10. Sixteen patients (80%) indicated that they would consider undergoing HIFU treatment again in the future.

When the clinicians compared the photographs obtained before and 12 weeks after treatment, they could choose appropriate post-treatment images in 15 cases (75%). They did not identify any difference between the photographs before and 12 weeks after the treatment in five cases, and none of the clinicians chose wrong post-treatment photos. Therefore, a score of 1 was assigned to each of the five cases. The clinicians rated the average score on the overall the improvement, skin tightening of the eyelids, and improvement of crow's feet as 2.30 (mean: 2.30 ± 0.86 ), 2.15 (mean: 2.15 ± 0.81), and 2.16 (mean: 2.16 ± 0.93), respectively (Fig. 1).

After then it was assessed whether the ALL changed significantly 12 weeks after treatment ($p < 0.0001$). The mean ALL decreased at 12 weeks post-treatment compared with that at baseline (Fig. 2). The mean ALL was 18.3 ± 2.75 mm immediately after treatment and was 17.2 ± 2.69 mm at
week 12. The difference between the mean ALL at baseline and at 12 weeks after the treatment was 1.05 ± 0.94 mm (Fig. 3).

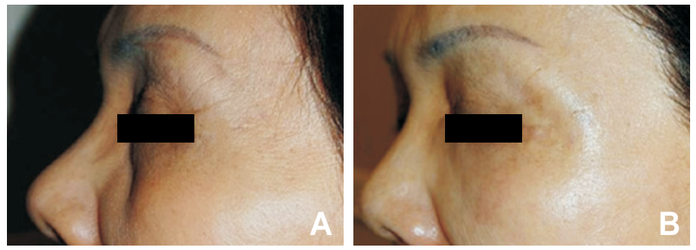


**Figure 1** Lateral view of a patient before (A) and 12 weeks after treatment (B) showing crow's feet.

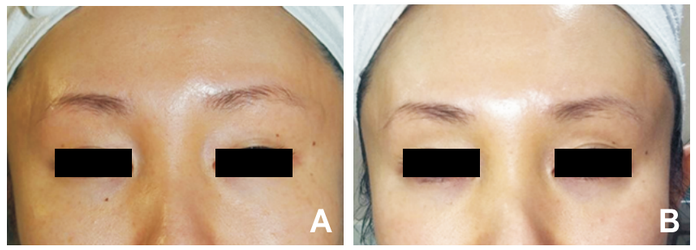


**Figure 2** Frontal view of a patient before (A) and 1
2 weeks after treatment (B).

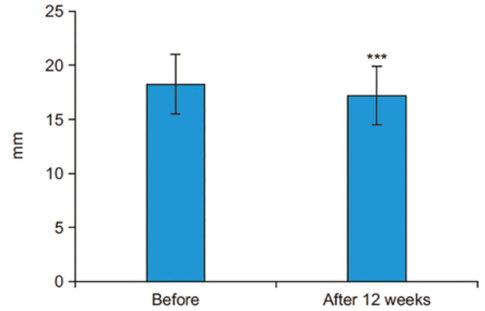


**Figure 3** The mean ALL before and 12 weeks after treatment (C). ALL: average lid length, which is the distance from the upper rim of the eye to the eyebrow along the midline between the medial and lateral canthus. ***Significant difference, $p < 0.0001$ vs before using paired ttest.

## DISCUSSION

Various attempts have been made to treat eyelid sagging, which can lead to eyelid ptosis. Depending on the severity of the condition, surgical options such as Müller's muscle conjunctival resection, shortening of the levator palpebrae, or brow/frontalis suspension are used [10,12]. However, these surgeries lead to common complications such as scarring, infection, bleeding, over- or under-correction, and reduced vision. Therefore, noninvasive procedures such as fractional lasers, intense pulse light, and radiofrequency treatment, which are designed to enhance collage remodeling, have emerged [13,14]. Among the various noninvasive techniques, HIFU is a unique technique that can induce collagenesis by causing thermally induced collaged contraction and tissue coagulation without damaging the epidermis [15]. Many studies have reported favorable outcomes regarding the safety and efficacy of HIFU [16]. However, to the best of our knowledge, only a few studies have reported a positive effect of HIFU treatment on the perioral area [7,17]. Another study demonstrated that HIFU could be effective for eyebrow lifting [18] although their result

was achieved by treating only the forehead. Moreover, no study has investigated whether HIFU treatment can safely tighten the eyelids through direct application on the eyelids.

Therefore, in this study, it was assessed the effect of HIFU treatment on the periocular area (around the eye) and were particularly interested in determining the tightening effect of HIFU on the eyelids. The results of this study showed that HIFU was effective for the overall rejuvenation of the periocular area. Both the patients and clinicians evaluated the average 4-point scale score for the overall improvement as higher than 2 (2.35 and 2.30, respectively), indicating that a mild-to-moderate level of improvement was achieved by HIFU treatment. Some tightening and improvement of crow's feet were also reported by both patients and clinicians. Although the ratings by the patients were slightly higher than those by the clinicians, the difference was not statistically significant.

After examined the changes in the mean ALL of the patients, authors observed a significant reduction after the treatment, implying that HIFU had a tightening effect on the sagging eyelids.

Several studies have explained the mechanism by which HIFU induces skin tightening. After some changes in living tissues caused by exposure to high-intensity and highfrequency sound waves were reported as early as 1928, the biological effect of high-intensity acoustic waves has been investigated with the development of ultrasound imaging techniques. When ultrasound waves propagate through tissues, a portion of the wave energy is converted into heat energy. The heat energy increases the temperature of the targeted tissue to 60°C, which results in coagulation necrosis. Therefore, HIFU was initially applied in clinical practice for the treatment of tumors such as uterine fibroids and prostate, breast, liver, and esophageal tumors. Ultrasound waves cause thermal and mechanical effects [19]. In 2008, White et al. [20] first proposed the dermatological and aesthetic use of HIFU by examining cadaveric specimens after HIFU exposure. Histological analysis of the specimens after HIFU exposure showed marked collagen contraction at a given depth without affecting superficial thermal injury. After this observation, it was concluded that HIFU has significant potential effect on aesthetic facial rejuvenation [21], and subsequently, many commercially available HIFU devices have emerged in the market. Ultraformer is one of the noninvasive ultrasound device designed to remodel collagen and tighten and lift the face. A special feature of Ultraformer is its MF2 cartilage with a targeted depth of 2.0 mm and its slim design that allows clinicians to treat narrow and sensitive areas of the face such as the eyes and mouth. In this study, authors successfully treated all the participants with the Ultraformer HIFU device without significant complications. One concern with HIFU treatment is that the improper use of the device may damage a patient's vision. However, the application of corneal protectors and the pulling up of the eyebrow by the clinician to avoid any contact of the device with the conrea during treatment can successfully prevent the above risks. Similarly, stretching the lower eyelids downward, which expands the wrinkles and separates the lower eyelids from the cornea, makes the procedure easier and safer. By adhering to these safety tips, none of the participants experienced extreme levels of pain, discomfort in the conrea, or loss of vision. The only notable side effects reported were mild pain and erythema that lasted for 3-4
days.

Finally, it is worthwhile to address several limitations of this study. First, as authors were not able to perform histological analysis, the investigation of cellular changes that occur due to HIFU treatment was limited. Second, the small sample size of this study might have limited the statistically significant results authors obtained. Third, Ultraformer is yet to be approved by the FDA and the only FDA-approved device, Ultherapy (Ulthera, Merz Inc.) was not used in this study. Investigating whether Ultherapy can reproduce results similar to those in this study can increase the reliability of our study.

## CONCLUSION

HIFU treatment can be a feasible method to treat signs of aging in the periocular area, and it can tighten and lift the eyelids as well as improve crow's feet without causing serious complications.





## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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# Simultaneous Combination Treatment Using High-Intensity Focused Ultrasound and Fractional Carbon Dioxide Laser Resurfacing for Facial Rejuvenation

Hee Yong Kang | Eun Soo Park | Seung Min Nam

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Simultaneous Combination Treatment Using High-Intensity Focused Ultrasound and Fractional Carbon Dioxide Laser Resurfacing for Facial Rejuvenation

Hee Yong Kang | Eun Soo Park | Seung Min Nam | South Korea

Department of Plastic & Reconstructive Surgery, Soonchunhyang University Bucheon Hospital, Bucheon, Korea

Correspondence
Eun Soo Park
Department of Plastic and Reconstructive
Surgery, Soonchunhyang University Bucheon
Hospital, 170 Jomaru-ro, Bucheon 14584, Korea
Tel.: +82-32-621-5319
Fax: +82-32-621-5016
E-mail: peunsoo@schmc.ac.kr

**Background and Objectives:** High-intensity focused ultrasound (HIFU) can produce small zones of thermal damage. A HIFU procedure is non-invasive and it can achieve rejuvenation of facial skin. Fractional CO2 laser resurfacing delivers thermal damage to the pixilated columnar zone of the skin and so evoke collagen remodeling, the same as HIFU. In many cases, the patients who want rejuvenation with HIFU are also good candidates for cutaneous photorejuvenation such as can be accomplished via fractional CO2 resurfacing. If patients are treated in a single session by remodeling both the superficial and deep compartments of skin by using both modalities, then improvement in rhytides and tightening of sagging skin will optimize the aesthetic result.

**Materials and Methods:** Between May 2014 and January 2018, a total of 44 patients were treated
with combination HIFU and fractional CO2 laser resurfacing according to our protocol. First, the HIFU was applied to the entire face with an average of 300 treatment lines. Immediately after HIFU treatment, the ultrasound gel was washed off and then fractional CO2 laser resurfacing was performed. We evaluated the patients using 4-point grading scales. The clinician examined the skin for evidence of complications after the completion of treatment.

**Results:** All the patients' skin quality showed improvement. Further. the clinical results after duel modality treatment were substantially better than that after the use of either modality alone. The recovery times and the incidence of adverse events when quickly and consecutively performing both treatments were similar as compared to those with employing stepwise treatment. We encountered no complications whatsoever.

**Conclusion:** When compared with stepwise therapy, combination therapy with HIFU and fractional CO2 resurfacing offers better, safer and more effective clinical results. Thus, for targeting multiple layers of aging facial skin, this combination therapy can be safely performed in a single treatment session.

**Keywords**
Rejuvenation; Fractional CO2 Laser; High-Intensity Focused Ultrasound Ablation; Asian Continental Ancestry Group; Cosmetic Techniques

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## INTRODUCTION

Recently in older people, there has been increasing public concern about aging skin. The signs of aging skin are dermal collagen and elastin fragmentation, fibroblast dysregulation, abnormal production of collagen-degrading matrix metalloproteinases and decreased assembly of Type I collagen, appeared as skin laxity, rhytides, and fine lines.1,2

High-intensity focused ultrasound (HIFU) has been researched as a tool for the treatment of solid tumor, originally. 3 In recent years, HIFU was developed as effective and noninvasive skin rejuvenation treatment device. HIFU produces thermal injury at precise depths in the deep dermis to the SMAS layer while sparing superficial skin layer. This procedure can improve skin laxity and texture and have been preferred by patients who avoid invasive or surgical skin tightening.

Ablative fractional laser resurfacing with CO2 source represents preferred procedure in the treatment of aging facial skin. This technology delivers thermal injury into the epidermis and papillary dermis, causing wound healing process. Collagen remodeling and neo-collagenesis occurs at a more superficial level than HIFU and wrinkles and fine lines improve.

In author's experiences, most of patients who received HIFU treatment are also good indication of cutaneous rejuvenation such as fractional CO2 resurfacing. So author think if we treat with HIFU and fractional CO2 laser at the same time, entire skin layer to SMAS are remodeled simultaneously and occurred more improvement of aesthetic results than single modality treatment. Many studies about single modality's effectiveness have been reported, but study about combination treatment of these are rare, especially in Asian ethnics.

Herein, we report about therapeutic efficacy and safety of HIFU and fractional CO2 laser combination treatment to large number of aging Asian patients.

## MATERIALS AND METHODS

### Treatment procedure

This study was performed by retrospective review. Between May 2014 and January 2018, total 44 Korea patients were treated at Department of Plastic and Reconstructive Surgery of Soonchunhyang University Bucheon Hospital. Patient's Fitzpatrick skin types are III to V with skin laxity and wrinkles. Patients with history of other cosmetic procedure were excluded from this study. We use the HIFU (Ultraformer®, Classys Inc., Seoul, Korea) and fractional CO2 laser (Line-XelTM, United thech Inc.).

Analgesia protocols was performed with topical application of 5% lidocaine cream (EMLA, AstraZeneca, Sdertlje, Sweden) 60 minutes before treatment. Then immediately before the procedure, ointment was washed off with water and soap.

Next, a thin layer of ultrasound gel was applied to face. Operator situated HIFU transducer perpendicularly on the target face skin and pressed the transducer uniformly.

Authors used two types of transducer. First, treatment was applied by 4-MHz, 4.5 mm depth transducers with 0.7-1.0 J/mm2 to thick skin area like cheek and chin. Then 7-MHz, 3.0 mm depth transducers with 0.3-0.5 J/mm2 was used in thick skin area and relatively thin skin area like forehead, nose and periorbital area. Ultrasound pulses being delivered to individual line within 1-2 seconds. Distance between lines was maintained at 3 to 5 mm parallel position to the previous treatment line. HIFU was applied to the entire face with average 320 treatment lines. The number of HIFU lines delivered necessary for treatment varied with the individual's pain tolerance and the size of the face skin areas. 80% of total shots were applied to thick skin area; 40% of shots by 4.5 mm depth transducer and 40% of shots by 3 mm depth transducer. Remnant 20% of shots by 3 mm depth transducer were applied to thin skin area. After HIFU treatment, the ultrasound gel was washed off. A fractional CO2 laser was applied immediately to the face with 100-120 mJ fluence. The laser procedure was performed with a pulse duration of 100-180 μs with a distance of 0.8-1 mm, degree 1th. Initial laser was applied in square shape with a size of 25×25 mm. Then 10×10 mm size square shape laser was applied in random shot mode to remnant face surface. The clinical endpoint of treatment was the presence of slight erythema. Complete treatment time was average 15 minutes. After laser procedure, cool pack compresses and postoperative 4% hydroquinone and sunscreen were applied to treatment area. Color make-up was permitted after 1-2 weeks.





| Grading scale | Descriptive Parameter | Skin aging | | | |
|---|---|---|---|---|---|
| | | Rhytides | Laxity | Elastosis | Texture |
| 1 | Mild | Wrinkles in motion : superficial | Localized : NL or ML | Early, Minimal yellow hue | Mild irregularity |
| 2 | Moderate | Wrinkles at rest : localized, superficial | Localized : NL, ML, Jowls, SM | Yellow hue, Localized PO and malar EB | Rough in several localized areas |
| 3 | Advanced | Wrinkles at rest : multiple superficial, a few deep | Prominent : NL, ML, Jowls, SM | Yellow hue, multiple EB with little uninvolved skin | Rough with a few uninvolved skin |
| 4 | Severe | Wrinkles throughout : multiple deep | Marked : NL, ML, Jowls, SM | Deep yellow hue, extensive EB | Extensively rough |
| EB, elastotic beads; ML, melolabial; NL, nasolabial; PO, periorbital; SM, submental/submandibular. | | | | | |

**Table-1** Modified quantitative comprehensive grading scale

| Score | Rating | Definition |
|---|---|---|
| 1 | Worse | No improvement |
| 2 | Mildly improved | < 25% improvement |
| 3 | Improved | 25-49% improvement |
| 4 | Much improved | 50-74% improvement |
| 5 | Very much improved | 75% improvement or more |

**Table 2** Subject Global Aesthetic Improvement Scale (SGAIS)

| Characteristic | Value |
|---|---|
| Sex (female, male) | 30, 14 |
| Mean age (range) | 51.2 (38-63) |
| Fitzpatrick skin type | Type 3 : 23<br>Type 4 : 19<br>Type 5 : 2 |

**Table 3** Patients characteristics

### Evaluation

Digital photographs (Nikon D750, Tokyo, Japan) before and after 3 months were collected. For each photo camera settings and identical ambient lighting were maintained in a same photographic room. Treatment effect was evaluated by three blinded independent plastic surgeons. They evaluated paired before and after digital photographs by using the Modified Quantitative Comprehensive Grading Scale (MQCGS) (Table 1). Alexiades- Armenakas et al. extensively used Quantitative Compre hensive 4-point Grading Scale for evaluating laser and energy-based cosmetic

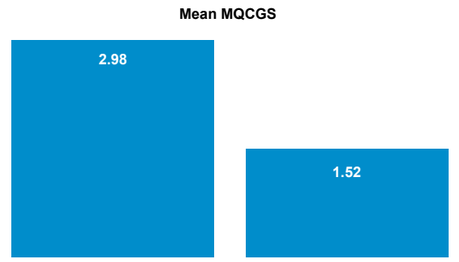


**Figure 1** Mean value of Modified Quantitative Comprehensive Grading Scale before and after treatment.

treatments.4-7 Author's modification was done by excluding categories of dyschromia, erythema-telangiectasia and keratosis, and combining integer and decimal scale. The improvement for each patient was calculated as the difference between the mean baseline and mean follow-up grades. Also subjective evaluation was assessed by using the Subject Global Aesthetic Improvement Scale (SGAIS) (Table 2) 3 months after treatment. Also at the same time, all subjects rated their satisfaction as excellent, good, fair or poor. The clinician examined the skin for evidence of edema, erythema, hypopigmentation, and hyperpigmentation after treatment.

### Statistical analysis

Statistical analyses of comparisons before and after the treatment by using Modified Quantitative Comprehensive Grading Scale were performed using the Paired t-test and SPSS statistical software (SPSS Inc., version 20.0, Chicago, IL, USA).

## RESULTS

This study included 44 Korean patients (30 women and 14 men), aged 38 to 63 years (mean, 51.2 years) and All 44 subjects returned for the 90-day follow-up. Patient's Fitzpatrick skin type are 3-5 type. Dermographics of patient is shown in Table 3. Skin quality was significantly improved after treatment, as demonstrated by the MQCGS, which was evaluated by 3 physicians blinded to the patients. (Fig. 1) The mean MQCGS scores were 2.98 (standard deviation 0.59) before treatment and 1.52 (standard deviation 0.37) 3 months after the treatment. After combination treatment, the mean MQCGS values decreased significantly ($p < 0.05$). All subjects showed clinical improvement after 3 months. Their average SGAIS was 3.93. Sixteen patients (36%) were assessed as having very much improvement, fourteen patients (32%) as having much improvement, nine patients (21%) as having fair improvement, and five patients (11%) as having mildly improvement at the 3-month follow up visit. No subject was reported to show no improvement. Post-treatment photographic finding was shown in Fig. 2, 3. Patient's satisfaction results were marked in Fig. 4. The percentage of 'Excellent' were the highest value and there are no patients who answered 'Poor'. Side effects included purpura, edema, erythema and serous discharge lasting 2 to 7 days (average 4 days) in all patients. No adverse effects or complications, such as scarring, infections, hypopigmentation and hyperpigmentation occurred in the present study. Recovery times and the incidence of adverse events was similar when compared with stepwise treatment.

**Figure 2** These are 56 years old female patient's photo. Left is oblique view before treatment. Right photo is oblique view after treatment 3 months. Improvement of periorbital and malar wrinkles and tightening effect of submandibular area skin are shown.

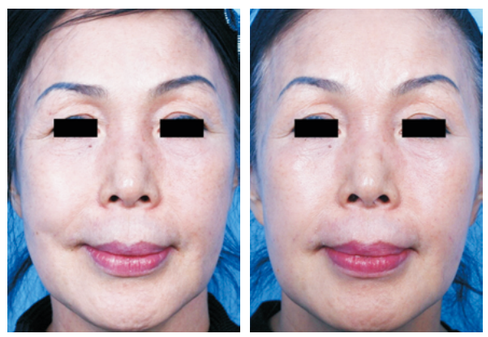

**Figure 3** These are 63 years old female patient's photo. Left is AP view before treatment. Right photo is AP view after treatment 3 months.
Improvement of periorbital wrinkles and tightening effect of forehead, nasolabial and submandibular area skin are shown.

## DISCUSSION

As human grows older, constantly aging process progressed in skin and its under structural tissues. The number of fibroblast and collagen synthesis also decreases and various skin appendages are also dropped. These aging process can present clinically as features of sunspots, uneven skin color, wrinkle and sagging skin.

"Rejuvenation" means restoration of youth and making looking young, including the treatment for the improvement of skin color, quality and elasticity of the skin as well as diminishing winkles and tightening the aging skin. The development of medical device for rejuvenation can be classified in many different ways.

In 2004, Manstein et al. introduced a fresh concept of rejuvenation utilizing a laser, now known as fractional photothermolysis.[8] In 2007, Hantash et al. introduced fractional laser based on fractional photothermolysis theory. 9 Many fractional lasers are now widely used in clinical practice of rejuvenation treatment. Especially, ablative fractional $CO_2$ laser causes vaporization, making areas of tissue coagulation spanning the epidermis and papillary dermis. Shrinkage of the collagen fibers with consequent shrinking of the skin and neo-collagenesis occurs and wrinkles and fine lines improve.[10-12] Compared to ablative fractional $CO_2$ laser, HIFU is a non-ablative rejuvenation technique. This uses the energy of ultrasound wave, which penetrates the epidermal layer and induces vibration of cellular molecules. These energy heats tissue to greater than 60°, producing small (< 1 $mm^3$) microthermal lesions at precise depths in the reticular dermis up to the SMAS layer while sparing epidermis and papillary dermis. This process provokes tissue coagulation, collagen denaturation and contracture with subsequent neocollagenesis and collagen structure remodeling.[13–15]

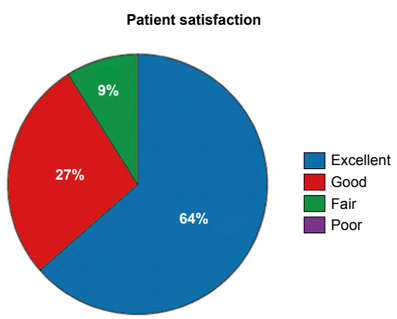


**Figure 4** Patient's satisfaction.

Rejuvenation using non-invasive or minimally invasive procedure like HIFU or fractional $CO_2$ laser is superior to surgical procedure in terms of pain, rapid return to daily life, short recovery time and low risk of adverse events. Because of these advantages, many patients who desire a skin-tightening procedure prefer noninvasive skin tightening to invasive or surgical skin tightening. However, these procedures cannot get dramatic effect in one time, so repetitive treatment at interval several months, or combination of other aesthetic procedures should be forced for ideal appearance. So authors hypothesize that if HIFU and ablative fractional $CO_2$ laser are performed in one time
without discomfort and post-treatment complications, patient's aging skin can more dramatically improves and patient's satisfaction will more increase because of timesaving and better aesthetic result.

In 2014, there was the study about combination treatment applying similar concept.[16] They used microfocused ultrasound device instead of HIFU and different fractional $CO_2$ laser device. They concluded combination treatment is safe and effectiveness procedure to patients. However, there was several limitations of this study, including lack of standardized evaluations and statistical proof. Besides, their patients consist of Caucasians. Asian people's dark skin is thicker and has more compact dermis than Caucasian's white skin, with the thickness being proportional to the degree of pigmentation.[17] Moreover dark skin types have more cornified cell layers and greater lipid content compared to white skin types.[18,19] So the experience gained from applying similar treatment protocols in Caucasians has been found not to be totally compatible to Asian skin. Thus, we start study about effect and safety of combination treatment to Asian skin using different devices.

Each modality's rejuvenation effects were different according to target layer. However, in combination treatment multiple layers were addressed at once, theoretically combination treatment's clinical results are more substantive than after the use of either modality alone. So When considering combination treatment, we should concern initially about complication like scarring, because the extensive heat load is applied to the underside and surface of the skin. But in our study data, there is no adverse effect. This shows combination treatment is a safe over the face of Asian, targeting both the deeper fibromuscular layer with HIFU and the more superficial dermis of the skin with fractional $CO_2$ laser.

Our study is the first study of combination treatment of HIFU and fractional $CO_2$ laser in facial rejuvenation using standardized evaluation methods with statistics. In our study data, standardized scales of skin quality (rhytides, laxity, elastosis and texture) were improvement with statistically significance by one treatment session and most of patient's subjective evaluation was high score. Also, most of patients were satisfied to this procedure, because procedure is safe, short-time and gives more dramatic effect than using each modality. Thus, we recommend our simultaneous combination treatment with HIFU and fractional $CO_2$ laser protocols in Asian face rejuvenation treatment.

Further study about combination treatment with HIFU and fractional $CO_2$ laser will be done for verifying the best treatment protocols, possibility of applying other anatomical site, difference by patient's race and comparing with other energy-based treatment device like radiofrequency, variable wavelength laser, etc.

## CONCLUSION

Simultaneous Combination Treatment with HIFU and fractional $CO_2$ laser on the face is a safe and effective method for targeting multiple layers of facial skin aging and can be safely performed in a single treatment session.

## CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest to disclose.

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# The efficacy of macro-focused ultrasound in the treatment of upper facial laxity: A pilot study

Rungsima Wanitphakdeedecha, M.D. | M.A., M.Sc. | Chadakan Yan, M.D.
Janice Natasha C. Ng, M.D. | D.P.D.S., Ya-Nin Nokdhes, M.D.
Ploypailin Tantrapornpong, M.D. | M.Sc., Thanya Techapichetvanich, M.D.
Sasima Eimpunth, M.D. | Woraphong Manuskiatti, M.D.

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The efficacy of macro-focused ultrasound in the treatment of upper facial laxity: A pilot study

Rungsima Wanitphakdeedecha, et al.

## ABSTRACT

**Background:** Recently, macro-focused ultrasound (MFU) has become a popular non-invasive aesthetic treatment for facial laxity. However, there are no studies done that evaluated the use of MFU with a 2.0 mm transducer for upper facial lifting.

**Objectives:** To evaluate the efficacy and safety of MFU with a 2.0 mm transducer in the treatment of upper facial laxity in Thai patients

**Methods:** This was a prospective, evaluator-blinded pilot study with 34 Thai patients diagnosed with mild to moderate facial laxity. Patients were treated with a single session of MFU with 2.0 mm transducer at the forehead, lateral and just below the eye area. Primary outcome was the clinical improvement of upper facial laxity graded by 2 blinded dermatologists at baseline, 1-week, 1-, 3- and 6-month follow-up. Objective measurements including eyebrow height, upper facial volume and textural irregularities were evaluated. Patients' self-assessment scores and adverse effects were also recorded.

**Results:** Out of 34 patients, 27 (79.4%) attended all follow-ups. Clinical improvement of upper facial laxity was observed as early as 1-week follow-up. Eyebrow height elevation was significantly increased at every follow-up (p=0.000) with an average of 1.22 mm at 6-month follow-up. Wrinkles improved significantly at 1-week and 6-month follow-up (p=0.002 and p=0.010, respectively). Skin roughness showed significant improvement at 6-month follow-up (p=0.004). Majority of the patients (53.6%) reported marked improvement at 3-month follow-up. No serious adverse event was noted.

**Conclusion:** MFU is a safe and effective treatment for upper facial laxity and skin textural irregularities in patients with mild to moderate degree of laxity.

## INTRODUCTION

Aging is an inevitable process that manifests differently depending on a patient's skin type, exposures, and genetics.[1] Most common dermatological signs of aging includes skin thinning, xerosis, wrinkles, hyperpigmentation and skin laxity.[1,2] It was found that Asians have denser dermal tissue compared to Caucasians, which likely contributes to a lower incidence of wrinkling and skin laxity.[2]

Facial laxity and wrinkles in the aging skin are common cosmetic concerns.[3] Rhytidectomy or facelift surgery remains to be the gold standard procedure but most would prefer less invasive modalities to avoid surgical complications, prolonged downtime and to achieve a subtler and natural appearance.[4] Minimally invasive procedures for facial laxity includes lasers, soft dermal fillers, neurotoxins, energy based devices (radiofrequency, ultrasound), fat grafting and thread lifts.[5-8] High intensity focused ultrasound (HIFU) technology has been used as a noninvasive surgical tool to treat a variety of solid malignant tumors since it offers less complications compared to conventional treatment modalities such as surgery.[9] In contrast, HIFU uses a much lower ultrasound energy to treat the superficial layers of the skin.[10] In 2009, micro-focused ultrasound with visualization (MFU-V) was approved by the US Food and Drug Administration (US FDA) for non-invasive brow elevation.[11] This ultrasound device is capable of heating the tissues at approximately 65°C, by producing discrete thermal injury zones(<1mm$^3$) at consistent depths depending on the transducer used.[12] The ultrasound energy delivered causes contraction of the denatured collagen fibers, neocollagenesis and collagen remodeling, which leads to lifting and tightening of the skin.[13] Available MFU-V are launched with various attached transducers that emit frequencies of 10.0 MHz, 7.0 MHz and 3.0 MHz with variable depths of 1.5 mm (dermis), 3.0 mm (deep dermis) and 4.5 mm (subdermal and superficial muscular aponeurotic system).[10] Currently, the new macro-focused ultrasound (MFU) with 2.0 mm transducer has been promoted to use for upper facial skin.

In a previous study, MFU-V with a 3.0 mm transducer was reported to lift the eyebrow height by 1.7 mm at 90

days after treatment when compared to baseline.[14] At present, there are no studies done using MFU with a 2.0 mm transducer for the treatment of upper facial laxity. The result might be different among different ethnicities because of variations in the aging characteristics and dermal thickness. The objective of this study was to evaluate the efficacy and safety of HIFU with a 2.0 mm transducer in the treatment of upper facial laxity in Thai patients.

## MATERIALS AND METHODS

This was a prospective, single-center, evaluator-blinded pilot study. A total of 34 Thai patients, male or female, age range between 30-50 years old, Fitzpatrick skin types III-V and diagnosed with mild to moderate facial laxity were included in the study. Exclusion criteria included patients who are pregnant or lactating, have pacemaker or metal implantation, facial surgical scar, history of keloid or hypertrophic scar formation, history of botulinum toxin or filler injection in the last 2 weeks before the study, history of thread lift, have ptotic fat, history of herpes simplex infection, history of active or systemic infection, who received non-steroidal anti-inflammatory drug (NSAID), aspirin, steroid, heparin, vitamin K or E in the last 72 hours before the study.

All patients underwent a single treatment session using the MFU device (Ultraformer III, Classys Inc., Seoul, Korea) for upper facial laxity. Preoperatively, topical anesthetic cream (EMLA®, AstraZeneca, Wilmington, DE, USA) was applied for 40 minutes prior to the treatment with occlusion. Ultrasound gel was applied to the target site and the device was gently pressed perpendicularly to the skin surface. The forehead, under and lateral eye area were treated with a 2.0 mm transducer (5.5 MHz). The application involved 90 horizontal lines in the forehead. In the lateral eye area, 5 horizontal and vertical lines are applied on each side. In the under eye area, 15 horizontal lines are applied on each side. Thus, a total of 140 lines were delivered in each patient. The energy for the ultrasound pulse was 0.2 - 0.4 J with a range of pitch at 1.5 mm.

Postoperatively, the patients were instructed to apply cold compress to the treated area to reduce pain and inflammation. They were also advised to use broad spectrum sunscreen and to avoid extremely hot or cold exposure, or any laser or radiofrequency therapy throughout the study.

The primary outcome of the study was the clinical improvement of upper facial laxity using the quartile grading scale: 0= no improvement, 1= minimal improvement (1–25%), 2= moderate improvement (26–50%), 3= marked improvement (51–75%) and 4= excellent improvement (76–100%). Subjective evaluation of the photographs was graded by 2 blinded dermatologists at baseline, 1 week, 1-, 3-, and 6-month follow-up. All clinical photographs were taken with identical camera settings, lighting, and positioning using a Canon PowerShot G9 stand-off camera (OMNIA imaging System, Canfield Scientific Inc., Fairfield, NJ).

In addition, eyebrow height, upper facial volume, wrinkles and skin texture were objectively evaluated at baseline, 1 week, 1-, 3- and 6-month follow-up. The average eyebrow height was measured using ImageJ software, by calculating the average vertical distance from the highest point of the eyebrow to the level of both mid pupils in 5 positions per side (a; medial canthus, b; medial limbus, c; mid pupil, d; lateral limbus, and e; lateral canthus to the highest point of the eyebrow) as shown in Figure 1. The upper facial volume was analyzed using 3 dimensional photographs captured by Vectra H1 Imaging System® (Canfield Scientific, NJ, USA). Skin textural irregularities (wrinkles, skin roughness, melanin concentration) were analyzed using Antera3D® (Miravex Limited, Dublin, Ireland). Patients' self-assessment score was evaluated using the same quartile scale on every follow-up. Pain score during the treatment was rated using a 10-point visual analogue scale (VAS). Adverse events were also evaluated.

Repeated measure ANOVA and paired T-test were used for parametric distribution data. Friedman test and Wilcoxon signed ranked test were used for non-parametric distribution data. A p-value < 0.05 was considered statistically significant. The statistical analysis was performed using a statistical software (SPSS version 18.0; SPSS Inc., Chicago, USA).

This study was approved by the ethics committee of the Siriraj Institutional Review Board. Written informed consents were obtained from all patients prior to their enrollment in the study.



## RESULTS

Of all 34 patients recruited, 27 (79.4%) completed the follow-ups. Seven patients were not able to attend the 6-month follow-up. The demographic data of the patients enrolled were described in Table 1.

Subjective evaluation of the upper facial laxity by photographic evaluation by 2 blinded dermatologists using the quartile grading scale was presented in Figure 2. As early as 1-week follow-up, 64.7% had minimal improvement (0-25%) when compared to the baseline. At 1-month follow up, majority (82.4%) still had minimal improvement, which was consistent until the 3-month follow-up (67.6%). However, at 6-month follow-up, most (51.9%) showed no improvement (0%) when compared to baseline. The clinical improvement of the upper facial laxity after MFU treatment is presented in Figure 3.

The eyebrow height measurements taken using ImageJ Software were described in Table 2. The average mean difference in eyebrow height was significantly increased on all follow-ups when compared to the baseline (p=0.000). The average eyebrow height elevation was 1.51 mm at 1-month, 1.25 at 3-month and 1.22 mm at 6-month follow-up. There was an increasing in the upper facial volume from baseline compared to all follow-ups as presented in Table 3, although it was not statistically significant.

The evaluation of textural irregularities (wrinkles, skin roughness and melanin concentration) using Antera3D® were described in Table 4. There was a decreasing in the wrinkle index on all follow-ups when compared to the baseline, however it was significant only on 1-week and 6-month follow-up (p=0.002 and p=0.010 respectively). Skin roughness also showed significant improvement at 6-month follow-up (p=0.004). Melanin concentration showed no significant difference from baseline compared to all follow-up visits.

Patients' self-assessment was also recorded on all follow-ups. As early as 1-week follow-up, majority (46.4%) reported minimal improvement, which continued to increase at 1-month (46.4% moderate improvement) and 3-month follow-up (53.6% marked improvement). However, on the 6-month follow-up, there was a decline in the improvement score wherein majority (38.1%) had moderate improvement (Figure 4).

All patients developed mild erythema immediately after the treatment with spontaneously resolved at 1-week follow-up. No post-inflammatory hypo- or hyperpigmentation, bullous formation, scar, crusting, oozing and any serious adverse events were recorded in this study.

| Characteristics | Value (n=34) |
|---|---|
| Age, mean ± SD* | 35.41 ± 6.31* (range 20-49) |
| Sex, n (%) | |
| Male | 5 (14.7) |
| Female | 29 (85.3) |
| Skin type, n (%) | |
| III | 1 (2.9) |
| IV | 29 (85.3) |
| V | 4 (11.8) |
| Number of Lines 2.0 mm transducer | 32.29 ± 9.19 |
| Mean pain score | 3.03 ± 1.57 |

*SD, standard deviation

**TABLE 1** Demographic data of patients enrolled in the study.

| Follow-Up | Eyebrow Height Measurements | | |
|---|---|---|---|
| | Mean ± SD(cm) | Mean Difference(cm) | p-value |
| **Baseline** | 2.95 ± 0.45 | | |
| **1-week follow-up** | 3.05 ± 0.50 | 0.095 ± 0.015 | **0.000*** |
| **1-month follow-up** | 3.10 ± 0.48 | 0.151 ± 0.016 | **0.000*** |
| **3-month follow-up** | 3.08 ± 0.45 | 0.125 ± 0.016 | **0.000*** |
| **6-month follow-up** | 3.07 ± 0.46 | 0.122 ± 0.017 | **0.000*** |

*p-value compared to baseline with statically significant difference

**TABLE 2** Assessment of eyebrow height measurement using ImageJ Software.

| Follow-Up | Difference of volume compared to baseline ($mm^3$) | | |
|---|---|---|---|
| | Mean ± SD* | Median | p-value |
| **1-week follow-up** | 0.15 ± 0.77 | 0.131 | |
| **1-month follow-up** | 0.57 ± 0.76 | 0.288 | 0.18 |
| **3-month follow-up** | 0.45 ± 0.59 | 0.454 | 0.96 |
| **6-month follow-up** | 0.36 ± 0.63 | 0.166 | 0.372 |

*SD, standard deviation

**TABLE 3** Assessment of upper facial volume measurement using Vectra H1 Imaging System®

| Evaluation | Baseline | 1-week follow up | 1-month follow up | 3-month follow up | 6-month follow up |
|---|---|---|---|---|---|
| **Wrinkles** | 15.86 ± 3.72 | 14.83 ± 3.53 (p = 0.002)* | 15.51 ± 3.85 (p= 1.000) | 15.38 ± 4.15 (p= 0.702) | 14.97 ± 3.79 (p= 0.010)* |
| **Skin Roughness** | 16.07 ± 4.38 | 15.21 ± 4.35 (p=0.092) | 15.77 ± 4.52 (p= 1.000) | 15.57 ± 4.91 (p= 1.000) | 15.63 ± 4.28 (p=0.004)* |
| **Melanin concentration** | 0.673 ± 0.075 | 0.673 ± 0.073 (p= 1.000) | 0.671 ± 0.073 (p= 1.000) | 0.673 ± 0.079 (p= 1.000) | 0.665 ± 0.081 (p=0.745) |

*p-value compared to baseline with statistically significant difference

**TABLE 4** Assessment of wrinkles, skin roughness and melanin concentration using Antera3D®

## DISCUSSION

Upper facial aging involves progressive loss of volume, sagging of facial soft tissue, skeletal bone loss, decrease in skin elasticity, skin damage and wrinkles at the forehead and periocular area.[15] Currently, HIFU technology has become a popular non-invasive aesthetic treatment for lifting and tightening because of its excellent safety profile when compared to the gold standard, rhytidectomy.[16,17]

HIFU delivers highly focused energy that is deposited in the form of heat leaving the surrounding area unaffected. The lesion that it creates are targeted, predictable and reproducible in terms of depth, size, and shape based on hand-piece frequency and source conditions (power, exposure time, and energy).[18] A previous study concluded that HIFU delivers energy in a transcutaneous manner without damaging the skin surface since the biophysical properties of the skin (transepidermal water loss, temperature, hydration and erythema) did not change significantly after treatment and at long term follow up of 24 weeks.[19] Confirmation by histology shows that the skin tightening and lifting effect of HIFU is attributed to an increase in dermal collagen with thickening of the dermis and straightening of elastic fibers in the reticular dermis after treatment.[20]

In this study, we reported that there was an increase in upper facial volume, but no significant difference between each follow-up visits when compared to the baseline. The increase in upper facial volume indicated the eyebrow lifting effect of MFU (average of 1.51 mm and 1.25 mm at 1-month and 3-month follow-up, respectively). At 6-month follow-up, the average eyebrow height was 1.22 mm which highlights that the lifting effect of MFU was maintained until 6 months.

A study was conducted among 25 patients with facial laxity treated with MFU-V (3.0 mm transducer, 7 MHz) and the average eyebrow lift was 0.47 mm at 3-months follow-up and a 0.12 mm decrease from the baseline at 6-month follow-up.[21] The decline in brow lift after 3-months follow-up was also reported in our study, and according to the authors this could be due to possible volume loss caused by the thermal injury in MFU-V. Another study with 30 patients (86%) demonstrated an average of 1.7 mm eyebrow height elevation at 3-month follow-up after MFU-V (4.5 mm transducer, 7 MHz) treatment on the forehead.[14] The variability among the results could be due to the different transducers used in each study and the number of lines delivered to the area. It was demonstrated that higher frequency waves produce more shallow focal injury zones while lower frequency produces a greater depth of penetration with deeper thermal coagulation points.[13]

The difference between MFU-V and MFU used in this study was the transducers. MFU-V utilized 3.0 mm and 4.5 mm transducer at 7 MHz to deliver micro-focused beam in dermis resulting in coagulation at targeted areas. Each beam will create thermal coagulation point with 0.5 mm in diameter. [14,21] In contrast, 2.0 mm transducer with 5.5 MHz was used to deliver macro-focus beam to create coagulation in larger area to stimulate collagen remodeling effectively. Even though the depth of the transducer used in this study delivering the energy to more superficial dermis (2.0 mm vs. 3.0 mm or 4.5 mm), the side of thermal coagulation point created by the macro-focused beam of energy was larger when comparing to micro-focused beam (1.0 mm vs. 0.5 mm in diameter, respectively).

We also evaluated the quantitative findings of wrinkles, which improved significantly at 1-week and 6-month follow-up. The immediate effect is theoretically related to the tissue-swelling effect that occurs after ultrasound treatment. This was consistent with a previous study done wherein the mean wrinkles score reduction at 3-months follow-up was statistically significant (p = 0.0222).[21]

The mean pain score was 3.03 ± 1.57, which shows that the treatment procedure was well tolerated by the patients. To further optimize patient comfort during treatment, it was recommended to recline the patient at 30 degrees instead of lying flat to prevent the increase in vascular stasis to the head and neck, which may cause heat sinking and increased perception of pain.[22] Different pharmacologic modalities such as inhalation of 50% oxygen/50% nitrous oxide, oral diazepam (5-10 mg) 30 minutes before procedure, ibuprofen (800 mg), intramuscular injection of meperidine (50-100 mg), promethazine (50 mg) or ketorolac (60 mg) and regional lidocaine block were also recommended.[22]

Unlike other energy devices, focused ultrasound is a “color-blind” technology as the energy is not selectively absorbed by chromophores.[16] In our study, we found no significant increase in the quantitative melanin concentration of the patients, which could translate there was no occurrence of post-inflammatory hyperpigmentation. In terms of safety, all our patients developed mild erythema immediately after the treatment, which resolved spontaneously. This is a commonly reported transient adverse event of HIFU.[23] Other than that no serious adverse event was noted. These supports the finding that MFU with 2.0 mm transducer is safe in Asian skin types.

Limitation of this study were the small number of patients and having no control group since this was a pilot study. There were also drop-outs because of lost to follow-up after 6 months of treatment. Moreover, we used the quartile scale in grading the clinical improvement and patients’ self-assessment scores. The grading system commonly used to evaluate cosmetic results are the Subject Global Aesthetic Improvement Scale (SGAIS) and the Physician Global Aesthetic Improvement Scale (PGAIS) since it clearly defines the degree of improvement.[17,24]

We would recommend further studies to be conducted and to extend the duration of follow up, to assess if the results can be maintained for at least a year. Another study can be done to focus on histological data following 2.0 mm transducer ultrasound pulses.

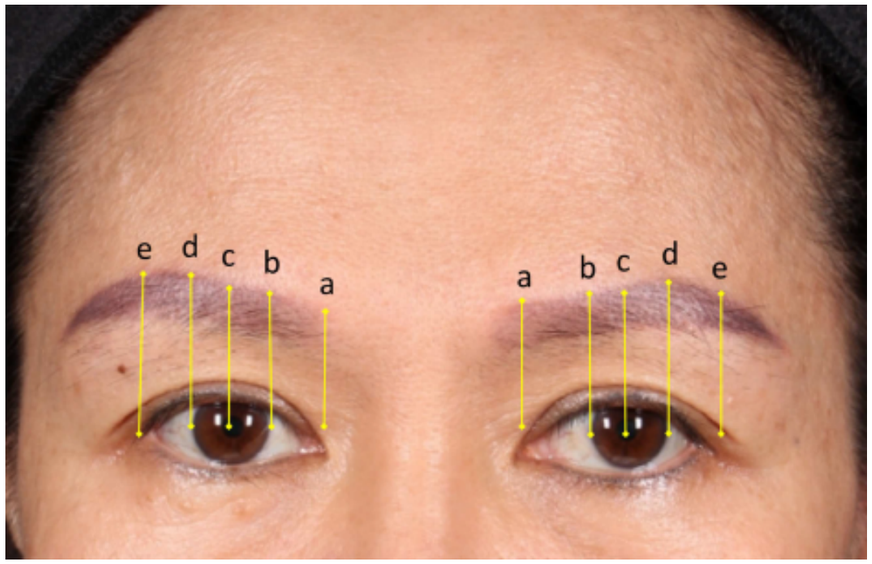
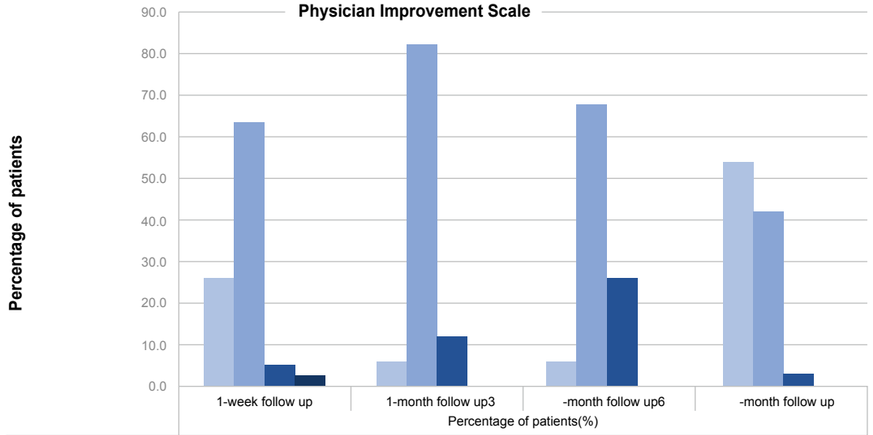



**Figure 1** Eyebrow height measurement using ImageJ software.




| | 1-week follow up | 1-month follow up3 | -month follow up6 | -month follow up |
|---|---|---|---|---|
| | Percentage of patients(%) | | | |
| 0 = No improvement | 26.5 | 5.9 | 5.9 | 53.9 |
| 1 = 1%~25% improvement | 64.7 | 82.4 | 67.6 | 42.3 |
| 2 = 26%~50% improvement | 5.9 | 11.8 | 26.5 | 3.9 |
| 3 = 51%~75% improvement | 2.9 | 0.0 | 0.0 | 0.0 |
| 4 = 76%~100% improvement | 0.0 | 0.0 | 0.0 | 0.0 |

**Figure 2** Physicians' evaluation of upper facial laxity by comparative evaluation of photographs from baseline to follow-ups.



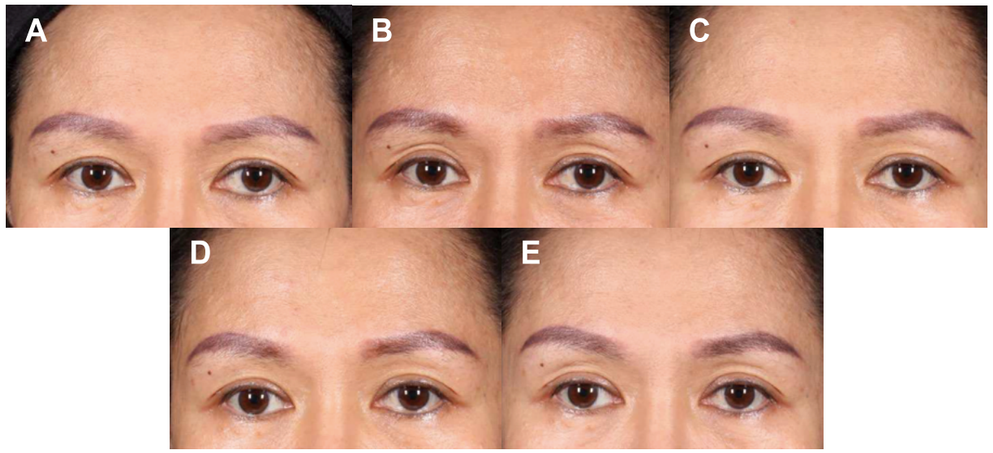
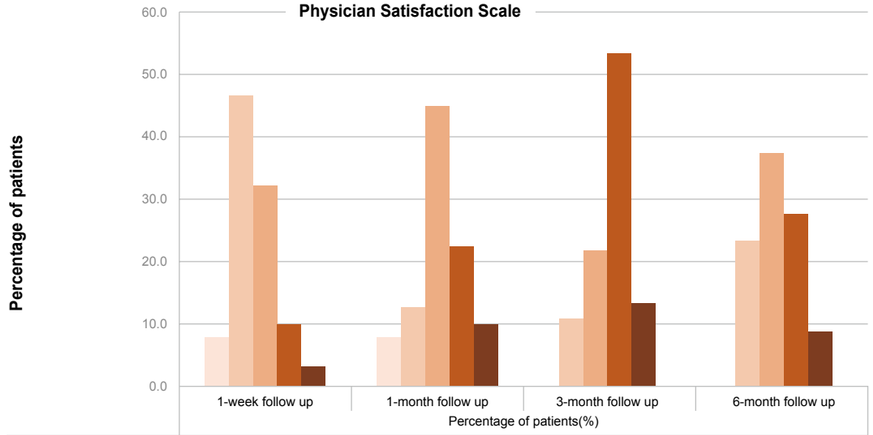



**Figure 3** Clinical improvement of upper facial laxity after 1 HIFU treatment from (A) baseline, (B) 1-week follow-up, (C) 1-month follow-up, (D) 3-month follow-up and (E) 6-month follow-up.




| | 1-week follow up | 1-month follow up | 3-month follow up | 6-month follow up |
|---|---|---|---|---|
| | Percentage of patients(%) | | | |
| 0 = No improvement | 7.1 | 6.9 | 0.0 | 0.0 |
| 1 = 1%~25% improvement | 46.4 | 13.8 | 10.7 | 23.8 |
| 2 = 26%~50% improvement | 32.2 | 44.8 | 21.4 | 38.1 |
| 3 = 51%~75% improvement | 10.7 | 24.1 | 53.6 | 28.6 |
| 4 = 76%~100% improvement | 3.6 | 10.4 | 14.3 | 9.5 |

**Figure 4** Patients' self-assessment on the improvement of upper facial laxity at baseline and follow-ups.

## CONCLUSIONS

The MFU device is a safe and effective treatment for upper facial laxity and skin textural irregularities in Thai patients.

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# A New Treatment Protocol of Micro-Focused Ultrasound for Lower Eyelid Fat Bulging

Hye Chan Jeon | Do-Yeop Kim | Seon-Pil Jin | Dong Hun Lee

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A New Treatment Protocol of Micro-Focused Ultrasound for Lower Eyelid Fat Bulging

Hye Chan Jeon | Do-Yeop Kim | Do-Yeop Kim | Dong Hun Lee


## ABSTRACT

**Background:** Micro-focused ultrasound (MFU) causes tissue tightening by producing thermal injury zones and is used to treat various age-related changes including lower eyelid fat bulging.

**Objectives:** To investigate the efficacy of a new treatment protocol of MFU for lower eyelid fat bulging.

**Materials and Methods:** We reviewed the medical records of all patients who began MFU for lower eyelid fat bulging from March 2017 to September 2018. MFU was performed in two steps to tighten the lower eyelid dermis and orbital septum. Data on age, sex, bulging severity, and the number of treatment sessions were obtained. Associations of these variables with treatment response were determined through an ordinal logistic regression analysis.

**Results:** Among 191 enrolled patients, 119 (62.3%) and 47 (24.6%) achieved fair and good responses, respectively. In the multivariable analysis, multiple treatment sessions (odds ratio [OR] 6.618; 95% confidence interval [CI] 3.242-13.513; P<0.001), moderate bulging (OR 4.328; 95% CI 1.755-10.671; P=0.001), and severe bulging (OR 7.570; 95% CI 2.537-22.585; P<0.001) were associated with greater treatment response. There were no serious adverse events.

**Conclusion:** The new treatment protocol of MFU is an effective and safe strategy for lower eyelid fat bulging.


KEY WORDS: Eyelids, rejuvenation, skin aging, ultrasonic therapy/methods

## INTRODUCTION

As aging progresses, lower eyelid fat bulging becomes prominent because of age-related changes in the soft tissue and bony orbit.[1] One of its major causes is the loosening of the orbital septum that supports orbital fat. Lower blepharoplasty can be performed for correction, but problems such as scarring, long recovery time, and overcorrection might occur. Thus, effective but non-to-minimal invasive methods for managing lower eyelid fat bulging have been required. Recently, non-surgical treatments such as ablative and non-ablative fractional laser, radiofrequency, and micro-focused ultrasound (MFU) have been used.[2, 3, 4, 5]

MFU produces discrete thermal injury zones to targeted areas, which results in shrinkage and tissue tightening.[6] Moreover, it can raise the temperature of the targeted adipose tissue while sparing the surrounding tissue, and no damage to intervening nerves or arterioles was observed within the path of the ultrasound pulse.[7] Given that the power density of the converging ultrasound beam is much lower as it passes through the path above the target point,[8] MFU is believed to be safe when used off-label for orbital fat treatment, and no serious adverse events have been reported in human eyelid studies.[5, 9]

However, when the orbital septum is deeply located, energy delivery to the orbital septum is limited in the conventional protocol.[5, 9] Also, the shape and location of orbital fat of most patients are not consistent in the supine position compared to the sitting position. In this study, we reported the efficacy of a new two-step protocol of MFU that tightens both lower eyelid dermis and orbital septum for correcting lower eyelid fat bulging.

## METHODS

### Study Population and Variables

We reviewed the medical records of patients with lower eyelid fat bulging who started MFU at the The Seoul Dermatology Clinic from March 2017 to September 2018. All patients were followed up until we confirmed that no further treatment is needed, until they were lost to follow-up, or until October 15, 2018 (date of scheduled data extraction), whichever arrived earlier. Patients who were lost to follow-up after the first treatment were excluded. Age, sex, and the number of treatment sessions were obtained from the medical records.

**Evaluating Bulging Severity and Treatment Results**

High-resolution digital photographs taken with a Canon EOS D30 camera (en face; Canon, Lake Success, NY, USA) were used to assess bulging severity and treatment response. Baseline bulging severity was scored from 1 to 5 using photographs taken before initial treatment, with 1 indicating mild bulging and 5 indicating most severe bulging. The severity scores were converted into a single ordinal variable by summing the number of individual scores by 3 independent dermatologists in the mild (3-6), moderate (7-10), and severe (11-15) categories. Treatment response was graded as follows by comparing photographs taken before the initial treatment and at the last visit: grade 0, no improvement; grade 1, <20%; grade 2, 20%-39%; grade 3, 40%-59%; grade 4, 60%-79%; and grade 5, 80%-100%. We also collapsed treatment response grades into a single ordinal variable by summing the number of individual grades by 3 dermatologists in the minimal (0-2), fair (3-5), and good (6 or more) responses. There were no missing data in this study because we had started to take photographs of patients with lower eyelid fat bulging at every visit as of January 2017.

The study protocol was approved by the Institutional Review Board of Korean National Institute for Bioethics Policy (P01-201903-21-001), and the requirement for obtaining informed consent was waived.

**Intervention**

We used the ULTRAFORMER III, SHURINK MFU device (CLASSYS INC., Seoul, Korea) with three different transducers. The EMLA cream (lidocaine 2.5% and prilocaine 2.5%; Astra Pharmaceutical Products Inc., Westborough, MA, USA) was applied to the treatment site 60 minutes before treatment. After the EMLA cream was wiped off, an ultrasound gel was applied to the skin.

In the first step, MFU was performed on the patients in the supine position using the L7-1.5 transducer (7 MHz, 1.5-mm focal depth) and either the L7-3.0 (7 MHz, 3.0-mm focal depth) or the L4-4.5 transducer (4 MHz, 4.5-mm focal depth) to tighten the lower eyelid dermis and orbital septum. Either the L7-3.0 or the L4-4.5 transducer was used depending on the depth of the orbital septum, which was measured before treatment using a handheld ultrasound device (UProbe-L5NC, Sonostar Technology Co., Guangzhou, China). To ensure that the orbital septum could be targeted by each shot, we applied proper pressure toward the infraorbital margin with the transducer during the procedure.

Moreover, in the second step, L7-3.0 and L4-4.5 transducers were used in patients in the sitting position to tighten the orbital septum. While the transducer was being used, patients were instructed to open their eyes and look upwards.

The energy per ultrasound pulse used at the first and second steps ranged from 0.10 to 0.20 J and from 0.3 to 0.5 J, respectively. The 25-mm-long exposure lines of ultrasound pulses were delivered parallel to one another with 3-5-mm spacing. Treatment lines were delivered to the skin located 2 mm below the lower eyelid margin to the inferior orbital rim, parallel to the lower eyelid margin. Patients receiving multiple sessions were treated at 3-week intervals.

**F-RAY**

To attempt a more precise evaluation of bulging severity and treatment response, additional photographs were taken using the F-RAY (BEYOUNG Co., Seoul, Korea). This device creates contour lines using the moiré phenomenon; thus, it is expected to enable more sensitive volume assessment (Fig. 1). Three dermatologists evaluated baseline bulging severity and treatment response with photographs taken with F-RAY in the same way as when evaluating with conventional digital camera photographs.

**Statistical Analysis**

Ordinal logistic regression analyses were used to evaluate associations between predictive factors and treatment response. Predictive factors showing univariable associations with treatment response (P<0.20) were included in a multivariable ordinal logistic regression model.

Interrater reliability for bulging severity and treatment response scores was assessed using Spearman correlation. Differences in the treatment response evaluation (conventional digital camera vs. F-RAY) were analyzed with the exact McNemar-Bowker test. All analyses were performed using SPSS statistics software, version 20.0 (SPSS Inc., Chicago, IL, USA). All statistical tests were two-sided and a P-value<0.05 was considered statistically significant.

## RESULTS

**Patients' Characteristics and Overall Treatment Response**

Detailed demographic and clinical characteristics of the patients are presented in Table 1. A total of 191 patients with lower eyelid fat bulging were identified and treated with MFU; of these, 162 (84.8%) were female. Patients' mean age at the time of presentation was 45 (range 20-73) years. The median treatment number per patient was 1 (interquartile range (IQR) 1-2).

The median bulging severity score was 9.0 (IQR 7.0-10.0), and median treatment response score was 4.0 (IQR 3.0-5.0). Overall, when evaluated by photographs taken with the conventional digital camera, 25 (13.1%) have had a minimal response, 119 (62.3%) a fair response, and 47 (24.6%) a good response (Fig. 2). The proportion of patients with good response tended to increase with the number of treatments (Fig. 3).

| Variable | All patients (n=191) |
|---|---|
| Age, mean (range), y | 45.3(20.0-73.0) |
| Sex, n (%) | |
| Male | 29 (15.2) |
| Female | 162 (84.8) |
| Number of treatment, median (IQR) | 1.0 (1.0-2.0) |
| Bulging severity score*, median (IQR) | 9.0 (7.0-10.0) |
| Treatment response score†, median (IQR) | 4.0 (3.0-5.0) |
| Mild (3-6), moderate (7-10), severe (≥ 11) | |
| †Minimal (0-2), fair (3-5), good (≥ 6) | |
| IQR, interquartile range | |

**TABLE 1** Demographic and clinical characteristics of patients

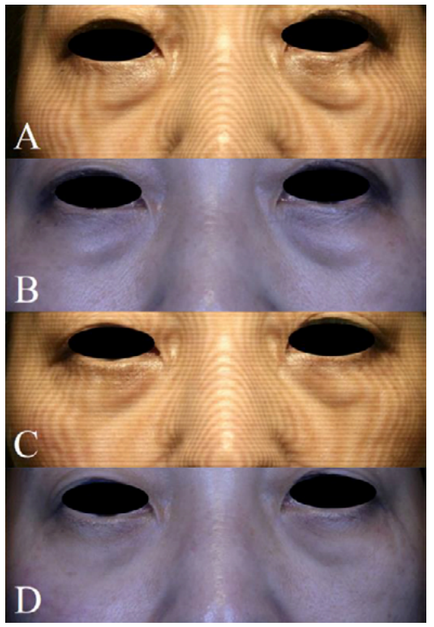


**FIGURE 1** Preoperative (A, B) and postoperative (C, D) photographs. (A, C) Photographs taken with F-RAY. Contour lines on skin surface assist volume assessment.

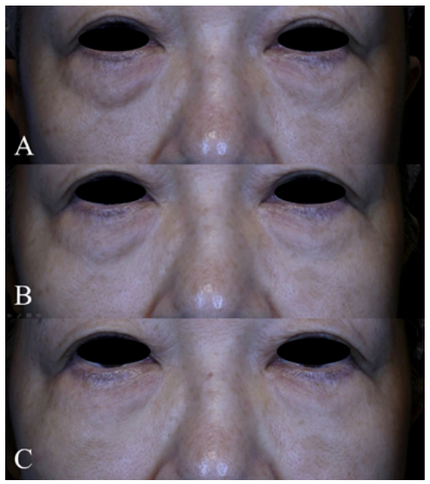


**FIGURE2** Preoperative and postoperative photographs using a conventional digital camera in a patient with a good response. Compared with pretreatment (A), photographs after the third treatment (B) and the seventh treatment (C) show gradual improvement.

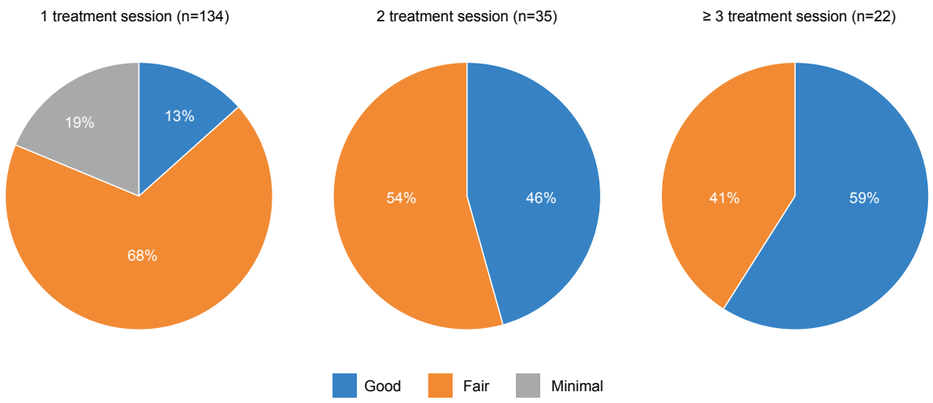


**FIGURE 3** Frequency of treatment response depending on the number of treatment sessions.

### Association Between Predictive Factors and Treatment Response

As shown in Table 2, the univariable ordinal logistic regression analysis revealed multiple treatment sessions, and more severe lesions were associated with greater treatment response (Table 2). There were no significant differences in the treatment response according to age and sex.

In the multivariable ordinal logistic regression analysis, two variables (treatment number and bulging severity) remained significantly associated with treatment response (Table 2). Multiple treatment sessions were significantly associated with greater treatment response (odds ratio [OR], 6.618; 95% confidence interval [CI] 3.242-13.513; P<0.001). Additionally, patients with moderate or severe lesions showed greater treatment response than patients with mild lesions (OR 4.328; 95% CI 1.755-10.671; P=0.001, and OR 7.570; 95% CI 2.537-22.585; P<0.001, respectively) (Table 2).

The study protocol was approved by the Institutional Review Board of Korean National Institute for Bioethics Policy (P01-201903-21-001), and the requirement for obtaining informed consent was waived.

### Comparison of Evaluation by Digital Camera and F-RAY

Average interrater reliability (Spearman) of bulging severity score and treatment response score evaluated by the conventional digital camera was 0.40 and 0.33, respectively. When evaluating using F-RAY, the average interrater reliability increased to 0.52 (P=0.139) and 0.39 (P=0.504), respectively, which was not significantly different. Figure 4 compares the treatment responses evaluated by a conventional digital camera and F-RAY. There were significantly more fair and good responses evaluated by the F-RAY than by the conventional digital camera (P=0.003). This suggests that a more sensitive and reproducible evaluation has been done when evaluating with F-RAY.

### Safety Assessment

The most common adverse events were pain and swelling (reported by approximately half of the patients), which were mild in severity. Other adverse events observed were bruising (reported by 5 patients), nodules (reported by 2 patients), ectropion (reported by 1 patient), and unilateral dacryorrhea (reported by 1 patient). All adverse effects were mild and resolved within 2 weeks. No serious adverse events were reported.

| Variable | Univariable analysis | | | | | Multivariable analysis | |
|---|---|---|---|---|---|---|---|
| | Minimal response (n=25) | Fair response (n=119) | Good response (n=47) | OR (95% CI) | P-(Value) | OR (95% CI) | P-(Value) |
| **Age,y, median(IQR)** | 44.0 (39.0-48.0) | 47.0 (36.0-53.0) | 49.0 (39.0-54.0) | 1.011 (0.984-1.039) | 0.418 | - | |
| **Sex, n(%)** | | | | | | | |
| **Female** | 22(88.0) | 100(84.0) | 40(85.1) | Reference 1.081 (0.489-2.390) | 0.8 | - | |
| **Male** | 3(12.0) | 19(16.0) | 7(14.9) | | 48 | | |
| **Treatment number, n(%)** | | | | | | | |
| **1** | 25(100.0) | 91(76.5) | 18(38.3) | Reference 7.720 (3.827-15.571) | <0.001 | Reference 6.618 (3.242-13.513) | <0.001 |
| **≥2** | 0(0) | 28(23.5) | 29(61.7) | | | | |
| **Bulging severity, n(%)** | | | | | | | |
| **Mild** | 9(36.0) | 18(15.1) | 0(0) | | | | |
| **Moderate** | 15(60.0) | 77(64.7) | 32(68.1) | Reference 5.266 (2.160-12.840) | <0.001 | Reference 4.328 (1.755-10.671) | 0.001 |
| **Severe** | 1(4.0) | 24(20.2) | 15(31.9) | 10.711 (3.736-30.734) | <0.001 | 7.570 (2.537-22.585) | <0.001 |

**CI, confidence interval; IQR, interquartile range; OR, odds ratio.**

**TABLE 2** Univariable and multivariable analysis of treatment response to MFU in lower eyelid laxity (n=191)

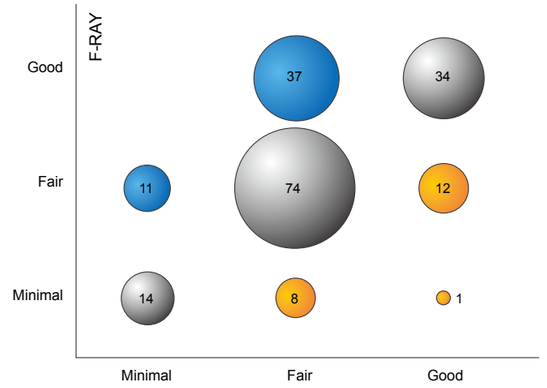


**FIGURE 4** Comparison of treatment responses evaluated by conventional digital camera and F-RAY (n=191). Significant asymmetry (P=0.003, Bowker test), i.e. significantly more fair and good responses evaluated by the F-RAY than by the conventional digital camera.

## DISCUSSION

This study investigated the efficacy and prognostic factors of a new two-step MFU protocol to tighten the lower eyelid dermis and orbital septum in patients with lower eyelid fat bulging. More than 80% of patients showed a fair or good response after undergoing the treatment with the new MFU protocol. Moreover, we showed that the clinical factors associated with the greater treatment response were multiple treatment sessions and moderate or severe bulging. Age and sex were not associated with the treatment response. In the first step, we employed a relatively lower energy (0.1-0.2 J) than 0.2-0.45 J from conventional protocols to reduce the risk of untoward side effects, and added the second step using a higher energy (0.3-0.5 J) with a 3.0 mm- or 4.5 mm-focal depth probe for effectively targeting the orbital septum as well as tightening the lower eyelid dermis. Also, looking upwards in the sitting position allows the orbital fat to bulge out so that physicians can treat it more precisely. In studies using conventional protocols of MFU for lower eyelid fat bulging, Suh et al.[9]

reported that 86.7% of patients were considered to have much improved or improved lower eyelid, and Pak et al.[5] reported an average improvement score of 3.45 and 3.25 on a scale of 0 (no involvement) to 4 (severe). It is difficult to compare the efficacy of the conventional and new treatment protocols directly because the evaluation was carried out 6 months after the single treatment session in previous studies, and the grading scale was different.

When treating the lower eyelid fat bulging with MFU, careful treatment is needed because the therapeutic response varies greatly depending on how precise the orbital septum is targeted.[5] Firstly, the target depth assessment through diagnostic ultrasound should be preceded to select probes for the appropriate treatment depth. During the procedure, the orbital septum becomes shallower as pressure increases; thus, proper pressure should be applied to adjust the target depth. Moreover, the probe should be placed parallel to the lower eyelid margin. If the probe is placed perpendicular to the lower eyelid margin, as Pak et al.[5] reported, the orbital septum would become deeper. To keep the depth change constant during the procedure on the orbital septum, it would be better to target the part that originates from the orbital rim.

It is also important to stay on the bone when treating the periorbital area, because the ultrasound waves will bypass any protective eye shield and can cause corneal damage.[10, 11] If the MFU is performed toward the inferior orbital rim, eye damage can be avoided without the need for an eye shield. In the second step, corneal damage was prevented by instructing patients to look upwards. Although one additional treatment step has been added, it was well tolerated with an adverse event profile similar to those in previous studies. Meanwhile, high-intensity focused ultrasound in bone metastasis is known to increase skeletal remodeling,[12] and a similar mechanism may contribute to improving lower eyelid fat bulging through the 'hammock effect'.[1]

Diagnostic ultrasound can also be used to distinguish other conditions that can be confused with fat bulging.[13] In dark circles with which the causes other than fat bulging are predominant, the effect of MFU is reduced and it may be better to perform other treatments. For example, treatment with a polynucleotide or hyaluronic acid can yield satisfactory results in dark circles due to the thin, translucent skin.[14]

We found that the number of treatment sessions was associated with treatment response. Improvement can be more pronounced with a longer observation period because the lipolysis and tightening process can last more than three months after a single session of MFU.[15] However, since the proliferative phase lasts for approximately 21 days in the wound healing process,[16] frequent treatments at 3-week intervals may lead to a rapid improvement.

In this study, more severe bulging led to better clinical outcomes. Although the severe group tended to receive more treatment sessions, the significance was still maintained in the multivariable analysis. In general, mild-to-moderate laxity is considered to be an ideal indication for MFU,[10, 17] but the satisfactory outcome can also be expected in severe cases.

We found that age was not associated with treatment response to MFU. This is consistent with two retrospective chart reviews showing that age was not associated with patient satisfaction after MFU.[18, 19] Although previous studies have reported that younger patients are more likely to have a good outcome, no statistical analysis was performed in these studies.[17, 20]

The evaluation using F-RAY was more sensitive, because the fluctuations of the skin surface can be evaluated more delicately with the aid of contour lines.[21] In addition, this device minimizes ambient light interference by using a blackout curtain and takes standardized photographs at a consistent angle by using cephalostats for the forehead and chin. It is also non-invasive; thus, it will be useful for the precise evaluation without any inconvenience. Our study had several limitations. Similar to other retrospective chart review studies, it is possible that there were unmeasured confounding factors, such as patient compliance. In addition, extent of fat bulging was not quantitatively measured. However, for more reliable results, we combined the scores of three independent dermatologists and also evaluated using F-RAY.

In conclusion, our results suggest that the new treatment protocol of MFU is effective and safe for lower eyelid fat bulging regardless of age and sex. Clinicians could consider additional MFU is effective and safe for lower eyelid fat bulging regardless of age and sex. Clinicians could consider additional MFU sessions if the improvement is not apparent after the first treatment.



## ACKNOWLEDGMENT

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## ACKNOWLEDGMENT

The authors report no conflict of interest.

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# High-Intensity Focused Ultrasound: A Satisfactory, Non-invasive Procedure for Crow's Feet Wrinkles

Gyu Sik Jung[1] | In Kook Cho[2] | Hyung Min Sung[3]

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MEDICAL LASERS

# High-Intensity Focused Ultrasound: A Satisfactory, Non-invasive Procedure for Crow's Feet Wrinkles

Gyu Sik Jung[1] | In Kook Cho[2] | Hyung Min Sung[3]

[1]GLAD Plastic Surgery Clinic, Daegu, Korea
[2]Lavian Plastic Surgery Clinic, Seoul, Korea
[3]V Plastic Surgery Clinic, Daegu, Korea

**Correspondence**
Gyu Sik Jung
GLAD Plastic Surgery Clinic, 31 Dongsung-ro 5-gil, Jung-gu, Daegu 41941, Korea
Tel.: +82-53-710-0103
Fax: +82-53-710-0133
E-mail: jksheart@naver.com
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**Background and Objectives:** High-intensity focused ultrasound (HIFU) has been developed as an effective, non-invasive, skin-tightening method in response to the increasing demand for improvements in skin laxity and tightening with minimal risk and recovery time. This study evaluated the efficacy and safety of HIFU for non-invasive skin tightening of crow's feet wrinkles, with the aim of determining how long the tightening can be maintained.

**Materials and Methods:** Between January and March 2019, 21 female patients with crow's feet wrinkles were treated with HIFU. The treatment involved 200 shots, three times every 2 weeks. Three blinded, experienced plastic surgeons and patients evaluated satisfaction at 2 weeks after the first procedure, 2 weeks after the second procedure, 2 weeks after the third procedure, and 6 weeks after the first procedure based on photographs according to the Global Aesthetic Improvement Scale (GAIS). The Friedman test was used to compare data.

**Results:** Of the 21 patients treated using HIFU, one was lost to follow-up for non-study-related reasons. Therefore, 20 patients were evaluated and ranged in age from 28 to 48 years. Plastic surgeons' GAIS scores were 2.6, 2.3, 1.7, and 1.3 and patients' GAIS scores were 2.6, 2.2, 1.8, and 1.4 at 2 weeks after the first procedure, 2 weeks after the second procedure, 2 weeks after the third procedure, and 6 weeks after the third procedure. No serious adverse effects were observed.

**Conclusion:** The aging face with crow's feet wrinkles can be improved by using HIFU, while minimizing epidermal and dermal injury.

KEY WORDS: Skin aging; High-intensity focused ultrasound therapy; Skin wrinkling

## 1. INTRODUCTION

Crow's feet wrinkles are characterized as laugh lines around the lateral aspect of the eyes. Static fine wrinkles around the eyes and dynamic wrinkles caused by movement of the orbicularis oculi muscle develop with aging. Non-invasive skin tightening is superior to invasive or surgical skin tightening in terms of rapid return to work, short recovery time, and low risk of adverse events. Because of these advantages, patients who desire a skin-tightening procedure prefer non-invasive skin tightening to invasive or surgical skin tightening.[1]

To meet patients' demand for non-invasive skin tightening, numerous devices besides the popular botulinum toxin procedure have been developed. Specifically, laser and radiofrequency devices have been developed to resolve skin wrinkling. Botulinum toxin treatment has a disadvantage in that it causes an awkward expression by reducing movement of the eyes. Recently, high-intensity focused ultrasound (HIFU) was developed as an effective non-invasive skin-tightening method. HIFU is able to heat tissue to greater than 60°C and produce a small thermal coagulation zone to reach the mid- to deep reticular layers of the dermis and subdermis while minimizing overlying papillary dermal and epidermal injury. The delivery of HIFU to a targeted zone in the superficial musculoaponeurotic system (SMAS) provokes the immediate contracture of denatured collagen, and initiation of neocollagenesis and collagen remodeling. This action of HIFU provokes non-invasive skin tightening and lifting of sagging facial skin.

However, certain factors including a lack of efficacy, persistence, and reliability have limited its replacement of invasive surgical procedures.[2,3] The purposes of this study were to evaluate the efficacy and safety of HIFU for crow's feet wrinkles, and to determine how long the tightening of crow's feet wrinkles can be maintained.

## 2. MATERIALS AND METHODS

Between January and March 2019, 21 patients with crow's feet wrinkles were treated with HIFU (I-SHURINK®; Classys Inc., Seoul, Korea; Fig. 1) using 5.5-MHz, 2-mm depth transducers (I-SHURINK MF2). Treatment was performed by the same surgeon and involved 200 shots, three times every 2 weeks. Informed consent was obtained from all patients, and the study was performed according to the Helsinki Declaration.

The exclusion criteria were cervicofacial, neurologic, or vascular facial disease; pregnancy or breastfeeding; local skin diseases that might alter wound healing; history of psychiatric illness, soft tissue augmentation material, cardiopathy, diabetes, facial or neck skin conditions, facial surgery; receipt of an antiaging procedure in the preceding 6 months; and active systemic or local infections.

### Procedure

Ten percent lidocaine, as a topical anesthetic ointment (EMLA, AstraZeneca, Sdertlje, Sweden), was applied to the periocular area for 30 minutes before the procedure. The ointment was washed off with mild soap and water immediately before the procedure. Then ultrasound gel was applied to the periocular area, and the transducer was placed firmly on the targeted skin surface and pressed uniformly to ensure complete contact with the skin. Treatment exposure was initiated (2-mm depth transducers; 0.4 J/mm$^2$), with a line of individual ultrasound pulses being delivered within approximately 2 seconds. Then, the transducer was slid to the next location and repositioned 2-mm laterally such that it was adjacent and parallel to the previous treatment line. Complete treatment of the face required 10 to 15 minutes. The ultrasound gel was washed off. Patients experienced mild redness and swelling that could persist for several days.

### Measurement

We compared the preoperative and postoperative measurements with the Global Aesthetic Improvement Scale (GAIS) at 2 weeks after the first procedure, 2 weeks after the second procedure, 2 weeks after the third procedure, and 6 weeks after the third procedure. Each scoring sheet was independently assessed by 3 blinded, experienced evaluators (3 plastic surgeons), and the plastic surgeons and patients' scores were compared.

### Statistical analysis

The Friedman test was used to compare the scores of patients at pre-treatment, and at 2 and 4 months after treatment. A p-value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS, version 20.0 (IBM Corp., Armonk, NY, USA).

## 3. RESULTS

All patients were treated using HIFU, and 1 patient was lost to follow-up for non-study-related reasons. Therefore, in our study, 20 female patients were evaluated and ranged in age from 28 to 48 years. There was no case of edema or erythema, linear striations, hypopigmentation, hyperpigmentation, ulceration, and erosion. There were also no adverse events, such as nerve or muscle dysfunction, severe pain, bruising, and bleeding.

Plastic surgeons' GAIS scores were 2.6, 2.3, 1.7, and 1.3 and patients' GAIS scores were 2.6, 2.2, 1.8, and 1.4 at 2 weeks after the first procedure, 2 weeks after the second procedure, 2 weeks after the third procedure, and 6 weeks after the third procedure. No serious adverse effects were observed during the 6-month follow-up period (Table 1, Fig. 2, 3).


**Figure 1** High-intensity focused ultrasound (I-SHURINK®).

## 4. DISCUSSION

HIFU burns tissue using high heat (65-100°C) at the focus where high-intensity ultrasound emergency is collected in one place. If you focus ultrasound energy at about 100,000 times stronger than the intensity of the ultrasonic wave used for diagnosis, heat is generated at the focus area. This is similar to a convex lens, which collects sunlight and generates heat at the focus area. The ultrasonic energy itself is harmless to the human body and generates heat only at the focus where the ultrasound energy is concentrated, so plastic surgeons can treat the lesion without the need for general anesthesia or use of a knife or needle.[4,5]

In order to minimize post-treatment adverse events, clinicians have developed various non-invasive skin-tightening procedures to induce collagen shrinkage and remodeling. Furthermore, ultrasonography is able to penetrate into the subdermal layer and SMAS, and induce thermal coagulation to avoid undesired post-treatment adverse events compared with carbon dioxide laser resurfacing.[3]

Ultrasound energy has characteristics that are suitable for skin lifting and tightening. First, it is believed that ultrasound energy can be transmitted into the deeper subcutaneous layer of the face or even the SMAS, and it is the most effective method for skin lifting and tightening. Second, both the epidermis and dermis can be protected from ultrasound energy during its transmission, reducing the risk of adverting cutaneous layers.[5]

**TABLE 1** Global Aesthetic Improvement Scale (GAIS)

| | 2 weeks after first procedure | 2 weeks after second procedure | 2 weeks after third procedure | 6 weeks after first procedure |
|---|---|---|---|---|
| Plastic surgeons' GAIS scores | 2.6 | 2.3 | 1.7 | 1.3 |
| Patients' GAIS scores | 2.6 | 2.2 | 1.8 | 1.4 |

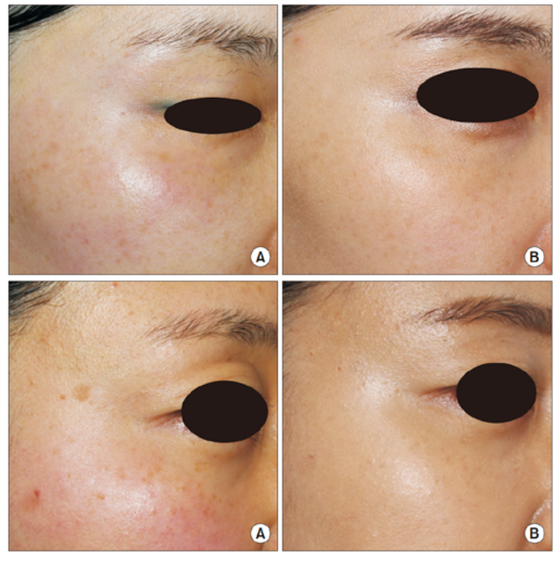


**FIGURE 2** Photographs of a 33-year-old woman. (A) Preoperative image. (B) Photograph after all three treatment sessions.

**FIGURE 3** Photographs of a 37-year-old woman. (A) Preoperative photo-graph. (B) Photograph after three treatment sessions.

HIFU uses high energy and is mainly used for non-surgical ablation of tumors. HIFU can also be used to ablate adipose tissue for body contouring. Micro-focused ultra-sonography (MFU) uses much lower energy to treat the superficial layer of the skin and is able to elevate the local temperature higher than 60°C to cause collagen contracture. When energy is targeted to discrete areas within the dermal and subdermal tissues, MFU induces discrete thermal coagulation zones while sparing adjacent non-target tissues. Additionally, the heat induces denaturation and contraction of collagen fibers in the subcutaneous fat layer.[6,7]

There is one more thing to watch out for when performing HIFU on the eye. Ask the patient to look at the opposite side of the procedure site. Have your eyes look down when you are working on your eyes, and when you are working under your eyes. The wrinkles on the surface of the skin of the site are also expanded, which makes it easier to perform the procedure, and even if the skin is deeply mistaken, the probability of reaching the eyeball surface is reduced.[8]

When HIFU is irradiated to the curved area around the eyes, blistering may occur when the skin is not 100% contacted. Make sure that it is exactly 90° and that one side of the cartridge does not float with your skin. In this case, an elevated striation may occur.

## 5. CONCLUSIONS

This study suggests that the aging face, with wrinkling and sagging, can be improved by HIFU, while minimizing injury to the epidermis and dermis. In addition, re-treatment is recommended at 3 months later to maintain the efficacy of the results.

## 5. CONFLICT OF INTEREST

The authors declare no conflicts of interest.





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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

Vasanop Vachiramon MD[1] | Wimolsiri Iamsumang MD, MSc[1] | Nongsak Chanasumon MD, MSc[1] | Kunlawat Thadanipon MD[1,2] | Korn Triyangkulsri MD[1] |

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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

Vasanop Vachiramon MD[1] | Wimolsiri Iamsumang MD, MSc[1] | Nongsak Chanasumon MD, MSc[1] | Kunlawat Thadanipon MD[1,2] | Korn Triyangkulsri MD[1]

[1]Division of Dermatology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand
[2]Section for Clinical Epidemiology and Biostatistics, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

**Correspondence**
Vasanop Vachiramon, Division of Dermatology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, 270 Rama VI road, Rajthevi, Bangkok 10400, Thailand.
Email: vasanop@gmail.com

## 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 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.

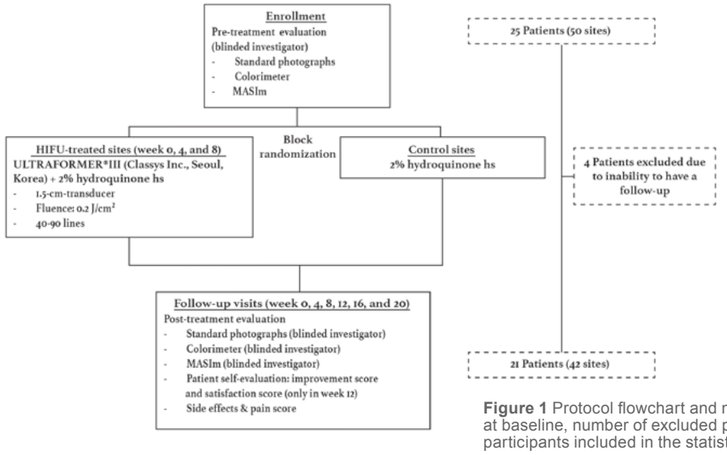


**Figure 1** Protocol flowchart and number of the participants at baseline, number of excluded participants, and number of participants included in the statistical analyses

### 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

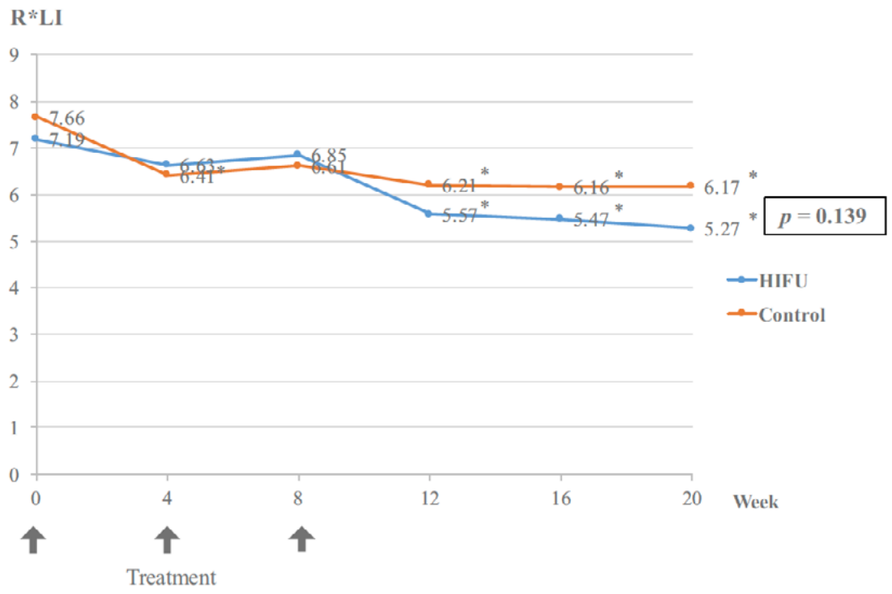


**FIGURE 2** Mean relative lightness index (RL*I) of HIFU-treated side in comparison with control side (*significant reduction compared with baseline P < 0.05)

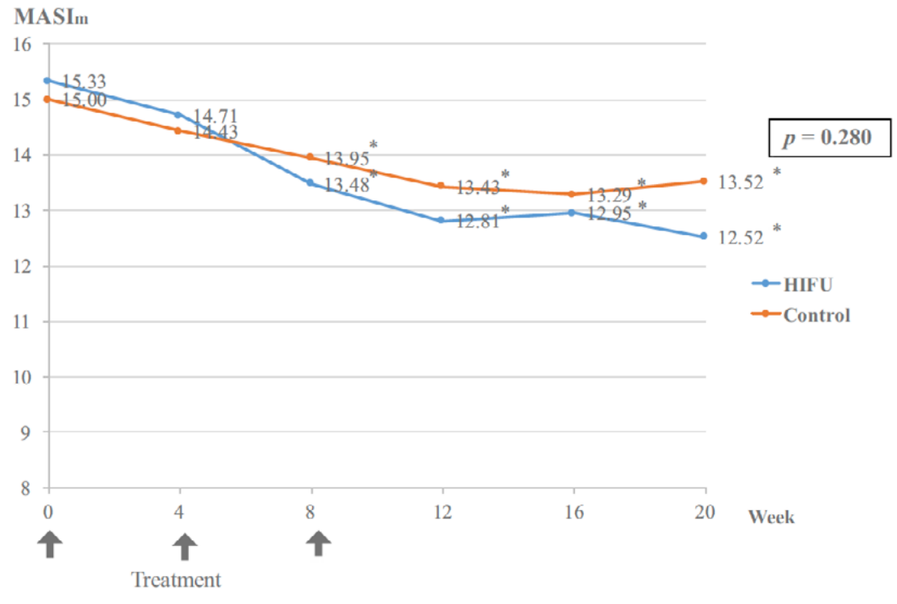


**FIGURE 3** Mean Melasma Area and Severity Index of the malar area ($MASI_m$) of HIFU-treated side compared with control side (*significant reduction compared with baseline P < 0.05)P < 0.05)





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

| 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





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

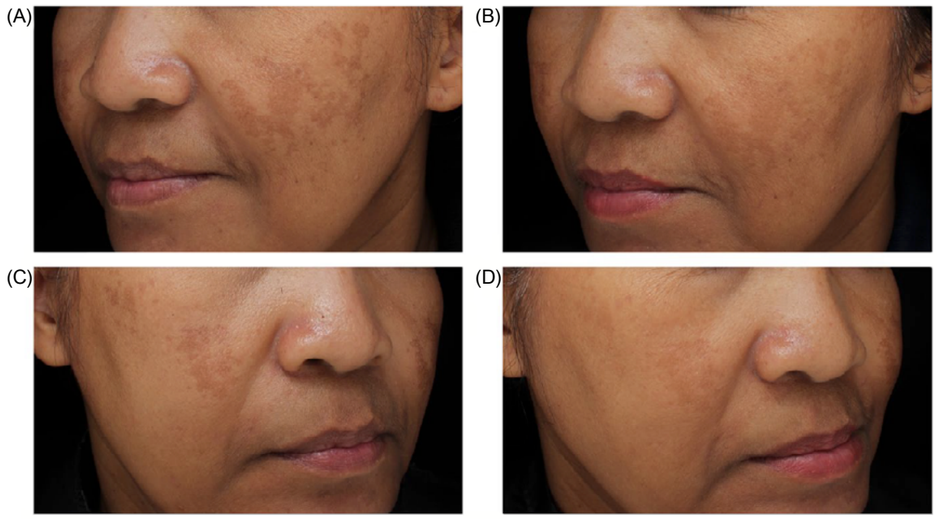


**FIGURE 4** Photographs of patient with melasma. (A) Control side at baseline, (B) control side at 12th week, (C) HIFU-treated side at baseline, and (D) HIFU-treated side at 12th week

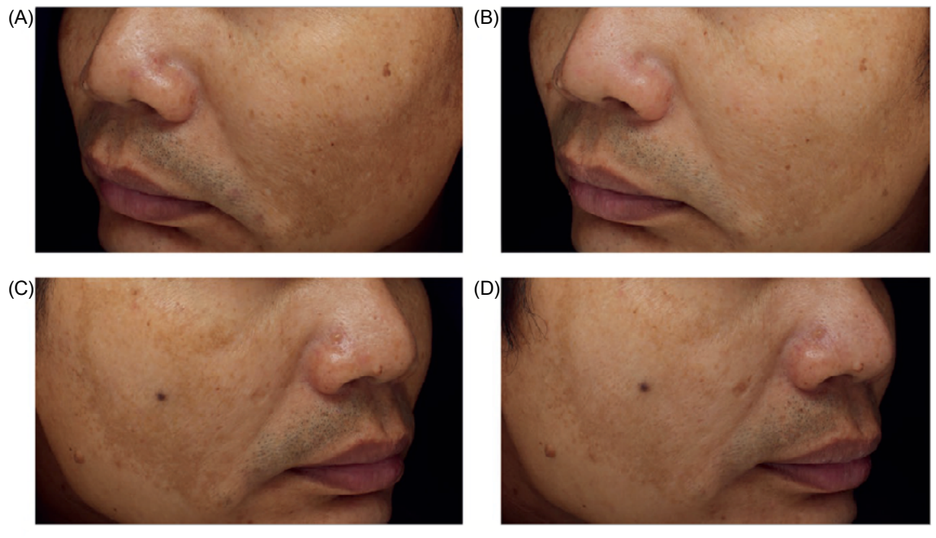


**FIGURE 5** Photographs of patient with melasma. (A) HIFU-treated side at baseline, (B) HIFU-treated side at 12th week, (C) control side at baseline, and (D) control side at 12th week





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## CONFLI CT OF INTEREST

The authors declare no conflict of interest.

## ORCID

*Vasanop Vachiramon* https://orcid.org/0000-0002-7328-939X

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# Effect of High-Intensity Focused Ultrasound on Eyebrow Lifting in Asians

Won Jong Oh | Hyun Jung Kwon | Sun Young Choi[1]
Kwang Ho Yoo[2] | Kui Young Park | Beom Joon Kim



Won Jong Oh | Hyun Jung Kwon | Sun Young Choi[1] | Kwang Ho Yoo[2] | Kui Young Park | Beom Joon Kim

Department of Dermatology, Chung-Ang University College of Medicine, [1]Department of Dermatology, Inje University Seoul Paik Hospital, Inje University College of Medicine, Seoul, [2]Department of Dermatology, Catholic Kwandong University International St. Mary's Hospital, Incheon, Korea

**Dear Editor** :

As skin aging progresses, the elasticity of the skin decreases and facial wrinkles are commonly seen. Various treatment modalities have been applied to treat wrinkles, yet patients are seeking more effective non-invasive methods with lower risk and minimal downtime. High-intensity focused ultrasound (HIFU) technology, originally used in cancer treatment to destroy cancer cells has emerged as an effective, non-surgical, tissue-tightening procedure . There are several reported results for face, neck, and body tightening with the HIFU device. However, there are few clinical trials that objectively present the efficacy and safety of application of HIFU to the forehead in Asian people. A total of 30 Asian patients (25 females and 5 males) were enrolled in the study. Study approval was granted by the Chung-Ang University Hospital Institutional Review Boards (C2013149[1109]). We received the patient's consent form about publishing all photographic materials. All patients were treated with HIFU device (Ultraformer; Classys Inc., Seoul, Korea) with a 7-MHz, 3-mm transducer to the forehead. Local anesthetic was applied to the target region. Depending on the width of the forehead, the HIFU device was applied along 9 to 11 vertical lines (Fig. 1). Each line consisted of 10 shots at an interval of about 5 mm. After application of ultrasound transmission gel, the HIFU probe was accurately placed with equal pressure to connect to the skin surface. Ultrasound imaging functionality was used to check whether the probe acoustically connected to the skin tissue for treatment and whether the depth of focus was geometrically on the reticular dermis at an intermediate depth. For treatment, 90~110 shots of ultrasound exposure were applied along the lines, and irradiation was performed for 2 seconds or more per ultrasonic pulse. Ultrasonic exposure in the forehead region took about 5 to 10 minutes in total.Before treatment, 4 weeks, and 12 weeks after treatment, standardized photographs of front and side views, rating scale values of pain, adverse events, physical findings, and patient satisfaction were recorded. We measured average eyebrow height (AEH) and maximum eyebrow height

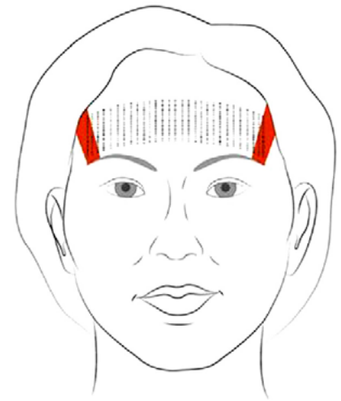

**Fig. 1.** Diagram showing proper distribution of line placement in the treatment region. Danger zones over the relative locations of the temporal branch of trigeminal nerves are highlighted in red.

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**Corresponding author:** Beom Joon Kim, Department of Dermatology, Chung- Ang University Hospital, 102 Heukseok-ro, Dongjak-gu, Seoul 06973, Korea. Tel: 82-2-6299-1525, Fax: 82-2-823-1049, E-mail: beomjoon@unitel.co.kr ORCID: https://orcid.org/0000-0003-2320-7621
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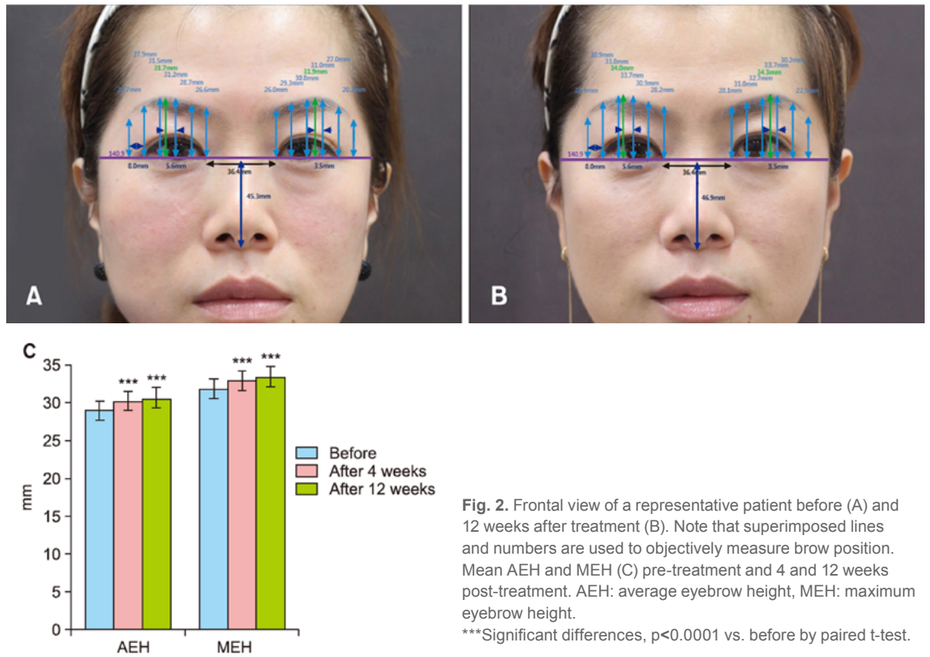


**Fig. 2.** Frontal view of a representative patient before (A) and 12 weeks after treatment (B). Note that superimposed lines and numbers are used to objectively measure brow position. Mean AEH and MEH (C) pre-treatment and 4 and 12 weeks post-treatment. AEH: average eyebrow height, MEH: maximum eyebrow height.
***Significant differences, p<0.0001 vs. before by paired t-test.

(MEH) of the patients. Both medial canthi were connected on images of the facial region seen from the front. On the medial canthi connection line, five points were assigned incrementally at intervals of 8 mm from the inside of the eye and the distance to the top of the eyebrow from each point was measured. The calculated average of the measured values was taken as the AEH, and the maximum distance from the medial canthi connection to the eyebrow was taken as the MEH (Fig. 2). Patients also rated their pain according to a visual analog scale (VAS). All adverse events, including local ones in the facial region, were included in a safety evaluation, and were recorded in the case report form and abnormalities were evaluated.

After application of the HIFU device, mean values of AEH and MEH significantly and progressively increased at 4 weeks and 12 weeks post-treatment compared with 0 weeks (p<0.0001). Mean AEH immediately after treatment (visit 1), at week 4 (visit 2) and week 12 (visit 3) were 29.08±3.17 mm, 30.22±3.24 mm and 30.64±3.28 mm, respectively. The difference in mean AEH from baseline was 1.14±0.29 mm at week 4 (visit 2–visit 1) and 1.56±0.30 mm at week 12 (visit 3–visit 1); both changes were significant (p<0.0001)(Fig. 2). Mean MEH immediately after treatment (visit 1), at week 4 (visit 2) and week 12 (visit 3) were 31.98±3.40 mm, 33.04±3.49 mm and 33.46±3.50 mm, respectively. The difference in the mean MEH from baseline was 1.06±0.34 mm at week 4 (visit 2–visit 1; p<0.0001), and 1.48±0.36 mm at week 12 (visit 3–visit1; p<0.0001) (Fig. 2). Immediately after treatment the mean VAS score for pain was 7.57±1.59, but no pain was reported at weeks 4 and 12. No permanent adverse effects were observed during the follow-up period. Skin tightening by delivery of non-ablative energy offers the promise of reduction of wrinkles and sagging with minimal downtime and no serious adverse events[2]. Collagen is the primary protein in the dermis, together with subcutaneous fat septae and the superficial musculo-aponeurotic system (SMAS). Ultrasound energy has specific characteristics that may increase its suitability for skin tightening. First, it is widely believed that energy delivery to the deeper subcutaneous layers of the face, or even the SMAS, is most effective in inducing skin tightening[3].



Furthermore, to the extent that this delivery can be divorced from secondary scatter and absorption in the epidermis and dermis, the risk of inadvertent cutaneous injury can be reduced. Besides ionizing radiation, ultrasound is the only type of inducible energy that can be delivered arbitrarily deeply into tissue in a selective manner[4]. Quantification of improved skin elasticity after treatment in a purely objective manner would be of great benefit for skin tightening procedures. As there is a limitation in scientific objectivity for subjective visual assessment from photographic documentation, eyebrow height was assessed using a standard measurement technique[5,6]. In this study, to ensure uniform assessment of change in eyebrow elevation, we used AEH and MEH.

Several studies have reported that HIFU resulted in an improvement of facial laxity. Alam et al.[2] have reported that a single ultrasound treatment of the forehead produced average brow height elevation of 1.7 to 1.9 mm. Suh et al.[4] have showed that 61.5% of eyebrows were lifted by at least 0.5 mm at 6 months. Compared with results of the above studies, our study demonstrated significant improvement of forehead skin laxity. In conclusion, we suggest that HIFU would be useful for lax eyelid conditions such as ptosis, as it had a positive effect on eyebrow lifting in Asian people. Future studies could use intense ultrasound probes focused deeper into the tissue to achieve greater tightening efficacy. Higher resolution diagnostic ultrasound imaging would provide better intraoperative visualization of the facial tissue layers, thus facilitating precise treatment and giving better results for skin laxity. Further studies are planned in the field of skin tightening, wrinkle improvement, and skin lifting on other sites of the face.

## CONFLICTS OF INTEREST

The authors have nothing to disclose.

## ORCID

Won Jong Oh, https://orcid.org/0000-0001-5201-7849
Hyun Jung Kwon, https://orcid.org/0000-0001-8376-2358
Sun Young Choi, https://orcid.org/0000-0003-0248-7708
Kwang Ho Yoo, https://orcid.org/0000-0002-0137-6849
Kui Young Park, https://orcid.org/0000-0001-5965-1754
Beom Joon Kim, https://orcid.org/0000-0003-2320-7621

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# Non-invasive Arm Fat Reduction

Logan William Thomas, MargitJuhasz, Lance Chapman, MicheleVanHal, RuzicaConic[1], AshleyMagovern[2], NatashaMesinkovska

Note: This article introduces new approaches for non-invasive procedures of the upper arm contouring including Low Level Laser Therapy, radiofrequency, high intensity focused ultrasound, radiofrequency, cryolipolysis to review those modalities and its efficacy. And the part of this article content is extracted as shown below.

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## Non-invasive Arm Fat Reduction

Logan William Thomas, MargitJuhasz, Lance Chapman, MicheleVanHal, RuzicaConic, AshleyMagovern, NatashaMesinkovska | USA

**ABSTRACT**

The demand for new approaches for non-invasive procedures of the upper arm is increasing. This review will present the most recent literature addressing modalities for arm fat reduction. Thirteen papers met inclusion criteria. The greatest arm circumference reduction (2.75 cm) is accomplished with the combination of cryolipolysis and shock therapy. Limited side effects are noted with each treatment modality. The most painful treatment is cryolipolysis. Physicians should be aware of the most common treatment modalities, new advances in devices, and possible side effects that may occur. There is a need to design and implement a universal patient satisfaction scale, such as the Global Aesthetic Improvement Scale. We recommend a standard approach to fat reduction measurement using three-dimensional imaging and suggest using US at a standardized location such as the midpoint between the olecranon and acromion processes. Although preliminary research suggests that non-invasive contouring of the upper arm is successful with limited adverse events, further research in this field will need to be completed to determine the long-term safety.

Key words: Arm contouring, cryolipolysis, high intensity focused ultrasound, low-level laser therapy, radiofrequency

## INTRODUCTION

Societal views on the perfect body aesthetic have as -sociated slimness with beauty; arm fat impacts how individuals perceive self-beauty and negatively impacts self-confidence.[1] Traditional approaches to arm fat refractory life style modifications include invasive surgical procedures such as liposuction [Figure 1], carrying risks such as post anesthesia adverse events, hospitalization, and prolonged post operative recovery;[2] the incidence of minor wound complications is 6.3%, and major morbidity is 6.8% 30 days after liposuction.[3] Non-invasive approaches to body contouring have become popular, with the development of novel devices and protocols. In a plastic surgery report from 2015, cosmetic surgical procedures have decreased by 10% since 2000, while minimally invasive procedures have increased by 158%.[4] Minimally invasive approaches have reduced concern for severe side effects and complications such as scarring, decrea-sed procedural discomfort and allowed faster recovery. Arm contouring is currently in demand with many approaches having been studied, and devices yielding promising results in the reduction of adipose tissue. In this review, we discuss evidence of non-invasive devices for arm contouring, including low level laser therapy (LLLT), high-intensity focused ultrasound (HIFU), radiofrequency (RF), and cryolipolysis.

### HIFU (High-intensity Focused Ultrasound)

HIFU uses ultrasonic waves and negative acoustic pressure to achieve results. Focusing acoustic energy at a singular point causes cell membrane disruption, cavitation bubbles, and acoustic energy is transformed into heat with temperatures 57°C.[19,20]Maintaining temperatures at a specific tissue depth, leads to adipose cell death and coagulative necrosis.[21] Histopa-thology demonstrates fat necrosis with multicellular inflammatory infiltrates and foreign body giant cells; 4–5-month post treatment 95% of adipocytes are destroyed.[19,20] Fortunately, surrounding tissue is unaffected. After adipocyte death, FFAs, inflammatory markers, and chemotactic factors are released, recruiting macrophages 3–4-day post-treatment; after 14–20 days, macrophages engulf and metabolize remaining cellular components. Inflammation and healing may take up to 90 days, with a clear reduction in subcutaneous fat on histology.[21,23] Three papers were identified using HIFU to tighten arm and/or elbow skin [Tab le 2]. Choi et al. describe the Ultraformer® III, Shurink (Classys Inc., Seoul, Korea) on six females, Asian patients. Using a Global Aesthetic Improvement Scale (GAIS) (-3–3 with-3 = very much worse and 3 = very much improved) investigators and individuals rated 100% “improvement” and at least an “improved,” respectively, 4 weeks’ post-treatment. Pain was ranked 5.17 ± 2.48 out of 10 (with 10 being the worst) immed-iately post procedure; no pain was noted at follow-up. [24] Rokhsar et al. demonstrate HIFU tightening skin over the elbow in 20 female patients. Physicians and patients noted a 94% and 81% improvement at follow-up, respectively. The mean pain score was 5.7 out of 10.[25]

# Efficacy of High Intensity Focused Ultrasound (HIFU) for Lifting and Tightening Lax Facial & Neck Skin

Sharmila Nayak

# Efficacy of High Intensity Focused Ultrasound (HIFU) for Lifting and Tightening Lax Facial & Neck Skin

Sharmila Nayak | India

## INTRODUCTION

To meet increasing public demand about facial wrinkles and laxity due to aging, various noninvasive skin tightening & lifting treatment options are utilized including chemical peeling, fractional laser, radiofrequency & high intensity focused ultrasound; however, the ideal treatment option has yet to be identified[1,2,3,4]. Recently, High Intensity Focused Ultrasound (HIFU) was used as novel treatment for therapeutic and cosmetic purposes[5,6]. Focused ultrasound is highly convergent and uses different frequencies of acoustic energy than medical ultrasound devices. The high-frequency focused ultrasound beam is allowed to target the subcutaneous tissues such as the superficial musculoaponeurotic system (SMAS) passing harmlessly through the upper layers of skin. This HIFU beam generate instant microthermal lesions where collagen around the focal point will reach over 65°C and be denatured & contract within milliseconds leading to additional de novo collagen synthesis and remodeling[7, 9, 10]. HIFU has been demonstrated to be safe and effective in numerous clinical trials as a noninvasive aesthetic treatment and has been cleared by the United States Food and Drug Administration (FDA) to noninvasively lift tissues in the eyebrow, neck, and submentum, and improve lines and wrinkles of the décollete[10].

In proposed study, efficacy evaluation of the Ultraformer III (HIFU) treatment was done on the basis of clinical improvement, adverse effects and patient satisfaction, these parameters were evaluated using clinical photographs and by a Subject Global Aesthetic Improvement Scale (SGAIS) and Physician Global Aesthetic Improvement Scale (PGAIS) scores at 3 months after treatment, in 20 patients older than 25 years of age.

## MATERIALS & METHODS

20 healthy subjects consisting of 15 women & 5 men between 25 to 60 years of age with skin laxity and facial wrinkles were enrolled into the study. Each subject was given informed consent & express their willingness to comply with all study requirement. All patients were of Fitzpatrick skin types IV and V. They were treated with HIFU device (Ultraformer III, Classys, South Korea) to the entire face, except for the nose and eyes, by using the following elliptical transducers, 4.5 mm focal depth (4 MHz), 3 mm focal depth (7 MHz) and 1.5 mm focal depth (7 MHz). The pitch (distance between the two high intensity focused ultrasound) was kept constant at 1.5 mm for all the focal lengths and it delivers a shot in less than 35 milliseconds. Before initiating treatment, prior assessment of subjects' skin tissue quality was done based on parameters such as age & gender, BMI & volume of subcutaneous soft tissue in the region to be treated. On the basis of assessment, a customized protocol was developed for the subjects. Mild thick layer of ultrasound gel was applied before starting the treatment on the skin. Treatment for each area was were given in three passes (horizontally, vertically and diagonal) to form a grid pattern which will give a proper lifting and will minimizes the skipped area. The whole face was treated with three different focal depths depending on areas where shoots were given (4.5 mm, 4 MHz; 3 mm, 7 MHz and 1.5 mm, 7 MHz). On the whole face 60% of area was covered by 4.5 mm transducer, 30% area by 3.0 mm transducer and 10% by 1.5 mm transducer.

Standardized two-dimensional photographs of each subject in frontal and 45° angle views, along with profiles from each side, were obtained using fixed camera and lighting conditions before, and 3 months after the treatment. All the subjects were evaluated based on a blinded qualitative assessment compared 90-days post treatment photos with baseline photos and quantitative improvement in skin tissue lift. The Subject Global Aesthetic Improvement Scale (SGAIS), Physician Global Aesthetic Improvement Scale (PGAIS) & Patient Satisfaction Questionnaires (PSQ) were also completed on 90 days post-treatment. Efficacy evaluation criteria's- the primary evaluation criteria is the overall improvement in skin lifting & tightening using blinded qualitative assessment of before & after treatment photographs. Secondary efficacy evaluation was done using PGAIS & SGAIS scale based on PSQ.

Using subject's 2D photographs taken on each follow-up visit quantitative assessment of brow & lower face tissue lift were done. Baseline & post-treatment photos were matched to ensure proper alignment. For lower face, an improved lift measurement

was defined as a submental lift ≥1.0mm. For the upper face, a lift measurement was considered improved if the eyebrow was raised ≥0.5mm.

## RESULTS

**Demographic information**

This study included 20 Indian patients (15 women and 5 men), aged 25 to 60 years (mean, 42.5 years) and All 20 subjects returned for the 90-day follow-up (100%). The number of shots delivered with the HIFU tightening device was 500±50.

**Efficacy evaluation results**

Among the 20 evaluated subjects, photos of 5 patients were excluded from blinded photography assessment, efficacy results were positive for 15 patients (75%).

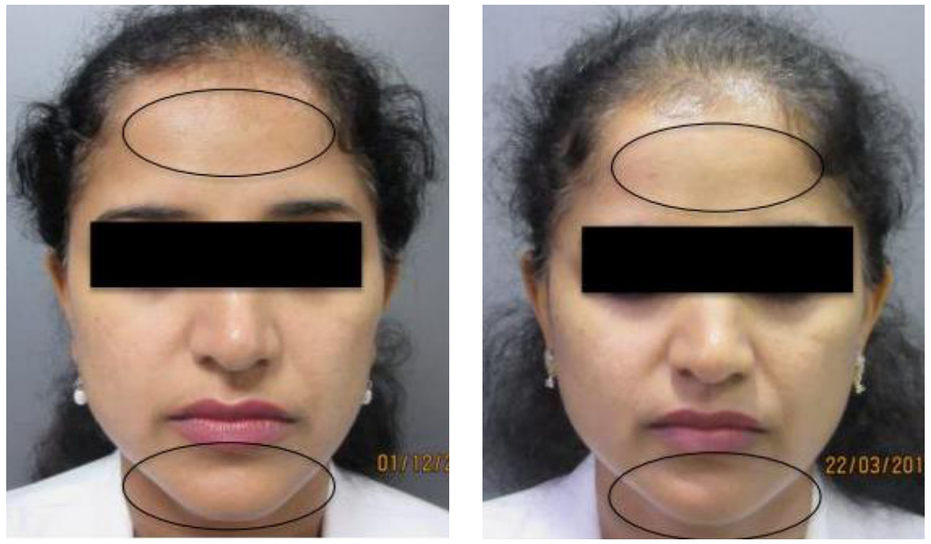


**Fig-1** Frontal view of a representative subject at baseline and post-treatment Day 90

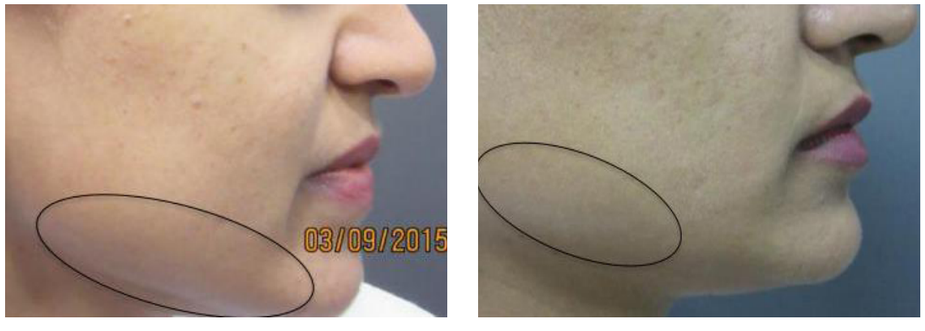


**Fig-2** Lateral view of a representative subject at baseline and post-treatment Day 90



Substantial improvement after 90 days post treatment can be seen in frontal & lateral views of the treated subjects in Fig-1 & 2 respectively. Results of the PGAIS reflects that 100 percent of the subjects were having aesthetic improvement after 90 days treatment, while SGAIS results indicated that 85 percent of subjects perceived aesthetic improvement after 90 days. Detailed PGAIS and SGAIS data are provided in Table 1.

| **Physician Scores** | **90 Days (N=20)** |
|---|---|
| Very much improved | 4 (20%) |
| Much improved | 10 (50%) |
| Improved | 6 (30%) |
| No change | 0 (0%) |
| Worse | 0 (0%) |
| All improved | 20 (100%) |
| | |
| **Subject Scores** | **90 Days (N=20)** |
| Very Much improved | 10 (50%) |
| Much improved | 3 (15%) |
| Improved | 2 (10%) |
| No change | 2 (10%) |
| Worse | 0 |
| All improved | 17 (85%) |

**Table-1** Global aesthetic improvement scale scores

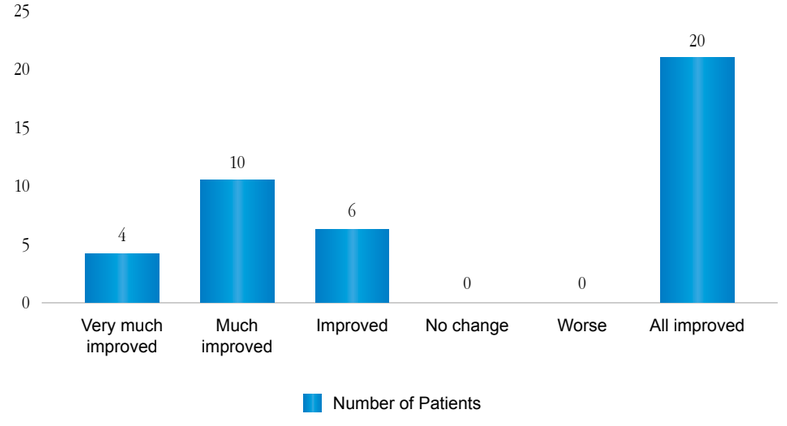


**Fig-3** Physician aesthetic improvement scale score (PGAIS)

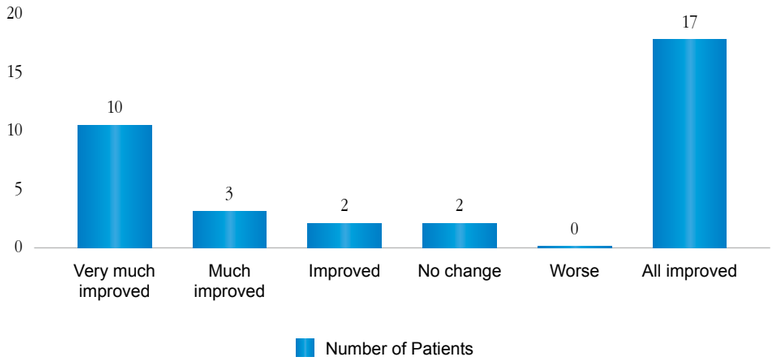


**Fig-4** Subject aesthetic improvement scale score (SGAIS)

## PATIENTS' SATISFACTION SCORE

Based on analysis of patient satisfaction questionnaires, 17 (85%) patients were found to have less sagging, 10 (50%) with less lines & wrinkles & 8 (40%) with smoother skin texture 8 (40%) (Fig-5).

We also assessed the efficacy and adverse effects 3 months after the treatment. Among 17 patients who replied, 5 patients answered that partial effects were still present in some areas.

| Parameter | 90 Days (N=20) |
|---|---|
| **Patient Satisfaction** | |
| Very Satisfied | 15 (75%) |
| Satisfied | 2 (10%) |
| Dissatisfied | 3 (15%) |
| Very Dissatisfied | 0 (0%) |
| Very Satisfied +Happy | 17 (85%) |
| | |
| **Improvement Noticed** | |
| Lines / Wrinkles | 10 (50%) |
| Less Sagging | 17 (85%) |
| More Even Skin Tone | 2 (10%) |
| Smoother Skin Texture | 8 (40%) |
| Other | 2 (10%) |
| No Improvement | 3 (15%) |
| **Would Continue & recommend treatment** | |
| Yes | 17 (85%) |
| No | 3 (15%) |

**Table-2** Patient satisfaction Questionnaires



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# Efficacy and Safety of Non-invasive Body Tightening with High Intensity Focused Ultrasound (HIFU)

E. J. Ko | J. Y. Hong | T.-R. Kwon | E. J. Choi | Y.-J. Jang
S. Y. Choi | K. H.Yoo | S. Y. Kim | B. J. Kim

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# Efficacy and Safety of Non-invasive Body Tightening with High Intensity Focused Ultrasound (HIFU)

E.J. Ko et al. | South Korea

E. J. Ko[1,2] | J. Y. Hong[1] | T.-R. Kwon[1] | E. J. Choi[1] | Y.-J. Jang[1,3] | S. Y. Choi[1,4] | K. H. Yoo[5] | S. Y. Kim[6] | B. J. Kim[1]

[1]Department of Dermatology, Chung-Ang University College of Medicine, Seoul, South Korea
[2]Department of Dermatology, Myongji Hospital, Seonam University College of Medicine, Goyang, Korea
[3]Department of Medicine, Graduate School, Chung-Ang University, Seoul, Korea
[4]Department of Dermatology, Seoul Paik Hospital, Inje University College of Medicine, Seoul, Korea
[5]Department of Dermatology, College of Medicine, Catholic Kwandong University, International St. Mary's Hospital, Incheon, Korea
[6]Classys Inc., Seoul, Korea

**Correspondence**
Beom Joon Kim, Department of Dermatology, Chung Ang University Hospital, 224-1 Heukseok-dong, Dongjak-ku, Seoul 156-755, South Korea.
Email: beomjoon@unitel.co.kr

## ABSTRACT

**Background:** Noninvasive skin- tightening devices have become increasingly popular in response to increasing demand for improvements in skin laxity and tightening with minimal risk and recovery time.

Objective: We evaluated the efficacy and safety of HIFU for skin tightening in the face and body.

**Methods:** A total of 32 Korean subjects enrolled in this prospective clinical trial. The subjects were treated with HIFU to both cheeks, lower abdomen, and thigh. Skin elasticity was measured before and after treatment using a Cutometer (CT575, Courage and Khazaka®, Cologne, Germany). Three blinded, experienced dermatologists evaluated paired pre- and post- treatment (week 4 and 12) photographs according to the Global Aesthetic Improvement Scale (GAIS). Participants also completed self- assessments using GAIS. Subjects rated their pain on a numeric rating scale (NRS) immediately, 7 days, 4 weeks, and 12 weeks after treatment.

**Results:** Skin elasticity measured via a Cutometer was significantly improved 12 weeks after treatment at all treated sites (P<.05). Both IGAIS and SGAIS showed significant improvements 12 weeks after treatment. Immediately after treatment the mean NRS score was 3.00±1.586, but no pain was reported at 4 and 12 weeks post- treatment. No serious adverse effects were observed during the follow- up period.

**Conclusion:** HIFU safely and effectively improves skin elasticity and clinical contouring of the face and body.

KEY WORDS: body tightening, high-intensity focused ultrasound

## 1. INTRODUCTION

The most common features of aging skin are laxity and loss of elasticity. As the skin ages, elastic fiber, collagen, and connective tissue in the dermis are reduced. Skin moisture and subcutaneous fat also decrease. There are many procedures to improve skin laxity, such as laser therapy, radiofrequency, botulinum toxin, fat autografts, and surgical lifting. Of these procedures, botulinum toxin and fat autografts are used for facial rejuvenation but are difficult to apply for improving body laxity. Radiofrequency and infrared laser devices which expose the dermis to controlled heat and stimulate neocollagenesis in dermis have inferior efficacy so that surgery still remains the treatment of choice in moderate to severe tissue laxity.[1] Although surgical face lifting is the most effective treatment to improve skin laxity, it is also a procedure that involves risks such as scarring, infection, nerve damage, inherent risks of anesthesia, swelling, and bruising.[2]HIFU technology was originally used as a non- invasive modality for selectively destroying tumor cells of internal organs by thermal coagulative necrosis for many decades.[3] HIFU was recently introduced as a new treatment modality for skin tightening and rejuvenation. The mechanism of HIFU is transcutaneous heat delivery to the deep dermis, subdermal connective tissue, and fibromuscular layer in precise micro-coagulation zones at consistent programmed depths without damage to the epidermis. This micro-coagulation is thought to cause gradual tightening of the skin through collagen contraction and remodeling.[4] HIFU first received approval for eyebrow lifting, but dermatologists are using the technology for many off-label applications, such as facial rejuvenation, skin whitening, and lipolysis. HIFU has been used

safely and effectively to treat facial and neck skin in a variety of skin types, but some studies have examined its use for the body, including our pilot study.[5–7] In this study, we sought to determine the clinical efficacy and safety of HIFU with novel transducers in both face and body regions.

## 2. SUBJECTS AND METHODS

Korean patients with skin laxity on the face, abdomen, and thigh were recruited for study entry. The study was approved by the Institutional Review Board of Chung-Ang University Hospital. Informed consent was obtained from all patients. Exclusion criteria were prior cosmetic or surgical treatments (e.g. laser, RF, surgical lifting, filler injections), skin infection or inflammation, pregnancy, skin diseases that may alter wound healing, open wounds, and scarring over the treatment area.

For pre-treatment preparation, we applied topical anesthetic cream to all treated areas including both cheeks, the lower abdomen, and the posterior thigh. The sizes of the involved areas were 5.0 × 5.0 $cm^2$ on each cheek and 7.5 × 7.5 $cm^2$ on each lower abdomen and thigh (Figure 1). We used a HIFU device (ULTRAFORMER III (SHURINK) CLASSYS INC., Seoul, Korea) with five different transducers: one basic transducer for facial skin tightening (MF1: 7-MHz, 1.5-mm focal depth), and four newly developed transducers for body skin tightening (MF3: 2-MHz, 3.0-mm focal depth, MF4: 2-MHz, 4.5-mm focal depth, MF6: 2-MHz, 6.0-mm focal depth and MF9: 2-MHz, 9.0-mm focal depth). Ultrasound gel was applied to the treated area and the transducer of HIFU was pressed perpendicularly, uniformly, and firmly to the skin surface (Figure 2). Treatment exposure was initiated with a line of individual ultrasound pulses. The pulse duration for each individual exposure ranged from 25 to 40 milliseconds. The 25-mm-long exposure lines of ultrasound pulses were manually delivered adjacent and parallel to one another approximately 3–5 mm apart. We treated subjects with several types of transducers appropriate to the thicknesses of facial and body skin. Three transducers (MF1, 3, and 4) were applied to the face and all five transducers (MF1, 3, 4, 6, and 9) were applied to the body. The energy per ultrasound pulse ranged from 1.0 to 1.5 J. When patients reported feeling pain, we reduced exposures to 0.1–0.3 J per time, and did not increase exposures up to 1.5 J. The treatment lines included a total of 120 shots for the cheek, distributing a total 537.6 J, and 450 shots for the abdomen and thigh, distributing a total 900 J. The time required for complete HIFU treatment of the face and body was over 40 minutes.

All patients were followed up at 4 and 12 weeks after treatment, at which times we obtained clinical photographs using consistent patient positioning, camera settings (Canon EOS 600D, high-resolution setting, 5760 × 3840 pixels, Canon Inc., Tokyo, Japan), and room lighting. Baseline and post-treatment photographs were randomly displayed, and independently evaluated by three dermatologists who were masked to the study protocol. Investigator Global Aesthetic Improvement Scale (IGAIS) scores were determined using side-by-side comparisons of 4-and 12-week post-treatment photographs to baseline. The subjects also evaluated the tightening effects using the Subject Global Aesthetic Improvement Scale (SGAIS)

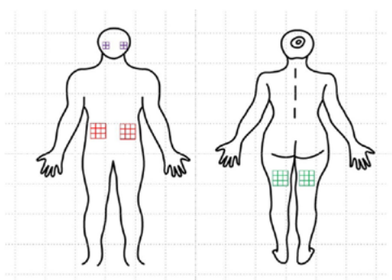

**Figure 1** Face and body treatment areas

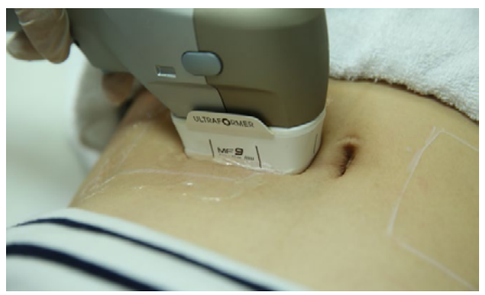


**Figure 2** The ULTRAFORMER III (SHURINK) HIFU device MF9 (2 MHz, 9.0 mm) tip applied on the abdomen (obtained from Classys Inc., with permission)





at 4 and 12 weeks post-treatment. We used the Cutometer (Courage+Khazaka Electronic GmbH, Cologne, Germany) to measure skin elasticity and objectively evaluate skin tightening. Among the cutometer-specific R values (R0–R9), the R7 value is the ratio of elastic recovery to the total deformation.

### 2.1 Statistical analyses

Statistical analyses were performed using SPSS version 21.0 for Windows (SPSS Inc., Chicago, IL, USA) and R version 3.2.3 (2015-12-10). We used Hochberg step-up methods to adjust values for multiple comparisons. and represents biological elasticity. Adverse effects were assessed at each visit after treatment. A numeric rating scale (NRS) was used to score pain immediately, 7 days, 4 weeks, and 12 weeks after the application of HIFU. Statistical comparisons before and after treatments were performed using paired t tests. Data are presented as mean±standard deviation. P values <.05 were considered statistically significant.

## 3. RESULTS

### 3.1 Efficacy

This study included 32 Korean patients (29 females and 3 males), aged 21–59 (mean±SD: 44.47±9.73) with Fitzpatrick skin types III and IV. All patients completed the 3-month study. The mean R7 value according to the Cutometer was significantly increased at 4 and 12 weeks post-treatment compared to baseline in all treated areas (Figure 3). The change of the mean R7 value at the thigh was 0.054±0.032, which represented the greatest change among the treated areas. IGAIS scores also showed good results (Table 1). Of the three treated areas, the cheek demonstrated the greatest improvements after treatment. At 4 weeks post-treatment, the improvement rates of subjects who were assessed as either improved (IGAIS score 1) or much improved (IGAIS score 2) were 96.9%, 84.4%, and 78.1% on the cheek, abdomen, and thigh respectively. At 12 weeks post-treatment, the improvement rate of the cheek area was reduced to 90.6%, but the body areas did not change significantly. Most subjects were satisfied with the results of treatment (Table 2). At 4 weeks post-treatment, all subjects rated SGAIS scores as greater than 1 on the cheek and thigh. The improvement rate assessed for the abdomen as greater than SGAIS 1 was 93.8%. At 12 weeks post-treatment, the improvement rates of cheek and thigh were reduced from 100% to 96.9%. However, the improvement rate of the abdomen increased to 96.8%.

### 3.2 Safety

The mean pain scores immediately and at 7 days after treatment were 3.00±1.586 and 0.031±0.177, respectively. The degree of pain decreased substantially within the first week post treatment. All patients were able to complete the treatment. No subjects

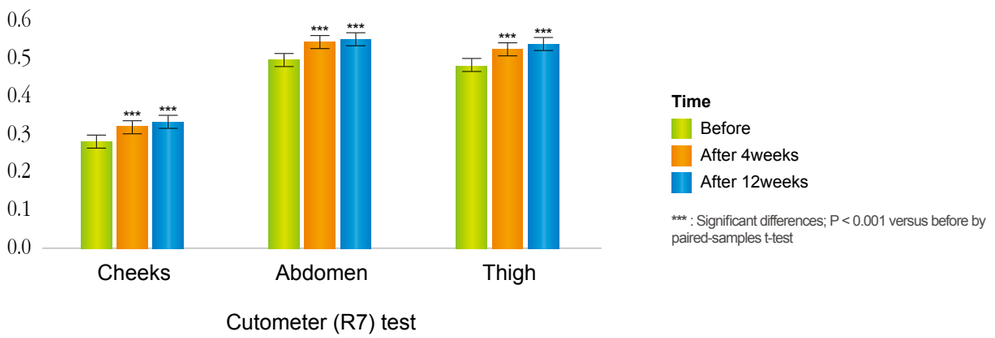


**Figure 3** Mean pre-and post-treatment R7 values of skin elasticity measured using Cutometers

| | | IGAIS | | | |
|---|---|---|---|---|---|
| | | 0 | 1 | 2 | 3 |
| Cheek | | | | | |
| Post-treatment(4W) | n | 1 | 29 | 2 | 0 |
| | % | 3.1 | 90.6 | 6.3 | 0 |
| Post-treatment(12W) | n | 3 | 29 | 0 | 0 |
| | % | 9.4 | 90.6 | 0 | 0 |
| Abdomen | | | | | |
| Post-treatment(4W) | n | 5 | 27 | 0 | 0 |
| | % | 15.6 | 84.4 | 0 | 0 |
| Post-treatment(12W) | n | 5 | 26 | 1 | 0 |
| | % | 15.6 | 81.3 | 3.1 | 0 |
| Thigh | | | | | |
| Post-treatment(4W) | n | 7 | 25 | 0 | 0 |
| | % | 21.9 | 78.1 | 0 | 0 |
| Post-treatment(12W) | n | 7 | 25 | 0 | 0 |
| | % | 21.9 | 78.1 | 0 | 0 |

0=No change, 1=Mild improvement, 2=Moderate improvement, 3=Significant improvement.

**Table 1** Investigator Global Aesthetic Improvement Scale(IGAIS)

| | | SGAIS | | | |
|---|---|---|---|---|---|
| | | 0 | 1 | 2 | 3 |
| Cheek | | | | | |
| Post-treatment(4W) | n | 0 | 13 | 13 | 6 |
| | % | 0 | 40.6 | 40.6 | 18.8 |
| Post-treatment(12W) | n | 1 | 10 | 10 | 8 |
| | % | 3.1 | 31.3 | 40.6 | 25 |
| Abdomen | | | | | |
| Post-treatment(4W) | n | 2 | 15 | 11 | 4 |
| | % | 6.3 | 46.9 | 34.4 | 12.5 |
| Post-treatment(12W) | n | 1 | 13 | 13 | 5 |
| | % | 3.1 | 40.6 | 40.6 | 15.6 |
| Thigh | | | | | |
| Post-treatment(4W) | n | 0 | 14 | 13 | 5 |
| | % | 0 | 43.8 | 40.6 | 15.6 |
| Post-treatment(12W) | n | 1 | 13 | 11 | 7 |
| | % | 3.1 | 40.6 | 34.4 | 21.9 |

0=No change, 1=Mild improvement, 2=Moderate improvement, 3=Significant improvement.

**Table 2** Subject Global Aesthetic Improvement Scale (SGAIS)





experienced persistent pain over the treatment areas at 3 months follow-up. Erythema was seen in up to 9.38% of the treatment sessions immediately post-treatment, but mostly subsided within 5 days (Figure 4). No patients showed surface injury or thermal damage on the treatment site. Ecchymosis was seen in up to 6.25% of treatment sessions immediately post-treatment. By 3 days post-treatment, all cases of ecchymosis had resolved. We observed no serious or delayed adverse effects during the follow-up period.

## 4. DISCUSSION

There are many noninvasive options of body sculpting, such as radiofrequency ablation, cryolipolysis, injection lipolysis, external low-level lasers, laser ablation, non-thermal ultrasound, and HIFU. Each of these treatments has no admission for treatment without anesthesia or analgesia and typically fewer complications than liposuction. However, with the exception of HIFU, patients have to visit the hospital several times for multiple treatments to achieve meaningful. Injection lipolysis and cryolipolysis have significant potential for AEs, which is largely unregulated and may cause significant pain, hematoma, allergic reactions, necrosis, scarring, panniculitis, and rapid release of lipids into the bloodstream.

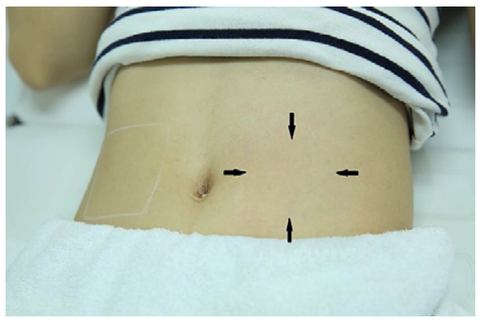

**Figure 4** Post-procedural mild erythema on the HIFU application site immediately after the treatment (black arrows). Erythema was resolved within 5 days

In contrast, previous clinical studies supported thermal HIFU for body sculpting have had no serious AEs including alterations in lipid profiles or other laboratory parameters[5-8]. Therefore, many clinicians are keeping an eye on the HIFU technique as purpose of body sculpting. Studies of HIFU facilitate the understanding of mechanisms of action for body sculpting. When used for body sculpting, HIFU delivers focused, high intensity ultrasonic energy to deep subcutaneous tissue, producing heat capable of effectively ablating adipocytes and thermally modifying collagen within the tissue matrix. In addition to local adipocyte necrosis, evidence of collagen remodeling from the thermal effects of HIFU has been observed.[9] Application of HIFU at a frequency of 1 MHz to adipose tissue leaves collagen fibers intact, but at frequencies of 2–3 MHz, diffuse contraction of collagen fibers occurs. Histological analyses performed after the procedure confirm that HIFU disrupts or denatures collagen fibers, resulting in new collagen formation accompanied by a general tightening of the septal fibers and skin[9]. Based on these results, newly developed transducers for application to body sites at a variety of focal depths (3.0–9.0 mm) are deemed to be suitable for body tightening. Also, we found no thermal damage on the skin surface of the HIFU treatment site. Kwon et al. has reported the temperature changes of the porcine model during HIFU procedure, which showed targeted subcutaneous fat to be around 70°C, while the skin surface temperature only went up to 33.1–35.6°C.[10] Therefore, we hypothesized that newly developed transducers could effectively and safely deliver HIFU energy deeper into the skin and eventually show body sculpting effects due not only to skin tightening but also to the reduction of subcutaneous fats. In this study, we used the Cutometer to evaluate the skin tightening effects of HIFU. Objective measurements of skin elasticity after laser, radiofrequency, and HIFU treatments are desirable. The use of uniform photographic documentation has improved, but there are often still inconsistencies in patient position and lighting. Physician-based grading systems are characterized by inherent elements of subjectivity. The purely objective quantification of results would be of great benefit for the evaluation of skin tightening procedures.

There are several reports describing the quantification of facial rejuvenation results using Cutometers. These include Shin et al., who used Cutometers to assess

the effectiveness of photographic rejuvenation with intense pulsed light (IPL).[11] Similarly, Naouri et al. assessed improvements in skin tightness after applying CO2 fractional lasers.[12] Ahn et al. demonstrated a stronger relationship between aging and skin elasticity parameters (R2, R7) than between aging and skin viscoelasticity parameters using Cutometers (R6),[13] while Kruger et al. made similar observations by conducting cutometric tests in a group of 120 females treating various parts of the body (cheek, neck, neckline, forearm, and back of the hand). They recommended the application of parameters R2 and R7 to evaluate the process of skin aging.[14] Thus, this study determined the R7 value from nine parameters of Cutometer.

In this study, we observed significant improvements in two body regions (abdomen and thighs) as well as the cheek when targeted for HIFU treatment. Adverse effects were limited to transient pain in most patients and occasional erythema or ecchymosis in some patients. HIFU can be safely and effectively used to improve the clinical appearance of the abdomen and thighs. Therefore, HIFU could meet current demands for significant, noninvasive skin lifting and tightening. Tightening and lifting of facial and body skin laxity can be achieved by inducing collagen fiber contraction and stimulating de novo collagenesis. By using newly developed transducers with different energy outputs and focal depths, HIFU treatment can be tailored to meet the unique physical characteristics of each patient.

## CONFLICTS OF INTEREST

Not declared.





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# High Speed Low-pain Micro Focused Ultrasound Tightening of the Lower Face and Neck

Adrian Lim, MD

## High Speed Low-pain Micro Focused Ultrasound Tightening of the Lower Face and Neck

Adrian Lim, MD | Australia

Dr Adrian Lim MBBS FACD FACP
Royal North Shore Hospital, uRepublic Cosmetic Dermatology and Veins NSW Australia

### INTRODUCTION

There is strong demand for non-surgical tightening procedures, especially to the jowl and neck areas, for a more youthful mandibular and neck contour (jawline). Popular procedures such as filler and botulinum toxin injections mainly target the face leaving the jowl and neck areas increasingly lagging with time. Non-surgical jowl and neck lifting procedures include skin resurfacing and various skin heating devices such as infrared, radiofrequency and micro-focused ultrasound (MFU).[1-4] Ablative resurfacing can tighten the skin but is largely limited by the recovery time and potential complications such as pigmentary alteration and scarring. On the other hand, non-invasive skin tightening devices are limited by subtle and inconsistent results, long treatment times and significant procedural discomfort.[5] In 2016, the Australian Therapeutic Goods and Services (TGA) approved a new high-speed, low-pain MFU device (Ultraformer 3) for skin tightening. This study is an evaluation of the safety, efficacy and patient satisfaction rate of Ultraformer 3 on lower face and neck laxity.

### Mechanism of action of Ultraformer 3

MFU can visibly tighten skin laxity in excess of 80% of cases.[6-8] MFU targets the SMAS (face lifting plane) for more natural and durable skin tightening. The delivery of the MFU is not associated with any epidermal injury and therefore does not require any recovery or down time. The focused and precise energy delivery is associated with significantly less side-effects such as burns, blisters, diffuse heating with collateral damage to adjacent epidermis or adipose tissue.

The Ultraformer 3 has a patented ultrasound focusing and delivery method that precisely targets tissue at adjustable depths of 4.5mm, 3mm and 1.5mm depending on the transducer cartridge selected, with corresponding frequencies of 4MHz, 7Mhz and 7 MHz respectively. In accordance to ultrasound physics, the higher frequency transducer cartridge corresponds to a more superficial focal depth. The Ultraformer 3 uses a proprietary mechanism enabling targeting a depth of 1.5mm without exceeding 7Mhz compared to conventional non-Ultraformer technology. The thermal injury zone (TIZ) is spaced between 1-2mm apart and the energy can be varied from 0.1J to 1.5J. The pulse duration for the 4.5mm cartridge range from 22ms (0.1J) to 33ms (1.5J) and the pulse duration for the 3mm cartridge range from 43ms (0.1J) to 65ms (1.5J). The relatively low pulse duration combined with adjustable energy allows precise and focused energy delivery without excessive collateral damage beyond the TIZ. The patented technology also enables faster treatment times with less procedural discomfort.

The objective of this study is to prospectively evaluate the efficacy and safety of the latest MFU (Ultraformer 3) for mandibular and neck contouring in patients with age-related laxity. We also undertook a patient satisfaction survey on the Ultraformer 3 procedure.

### METHODS

All 20 enrolled patients satisfied the inclusion/ exclusion criteria of: age 40 years or more, no previous skin tightening treatment in last 12 months, no neck or lower face botulinum injections for the last 6months and during the follow up period. Standardised face and neck photography was taken at baseline, immediately post-procedure and at subsequent follow-up at 6 weeks or more post-procedure. Patient satisfaction was assessed by a standardised survey performed at subsequent post-treatment follow-up visit (4 – 20 weeks). Procedural efficacy was rated by 2 blinded dermatologists examining baseline and post-procedural photos. The skin tightening treatment was administered by 2 trained registered nurses using the Ultraformer 3 (Classys, Korea). All patients were pre-treated with 60 minutes of compound anaesthetic to the lower face and neck and intra-operative chilled air cooling (Cryojet) and the additional options of using inhaled nitrous oxide if required. The treatment areas were: (A) lower face and (B) upper neck: submental and submandibular regions (avoiding thyroid). The method of treatment is as follows: (A) lower face: 2 passes – 2 columns down and 2 columns across – first pass is parallel to the jawline and second pass is perpendicular (90 degrees) to the jawline, and (B) upper neck: 2 passes parallel to the mandibular jawline (bilateral) and submental region.

## RESULTS

The patient demographics were: 19 females and 1 male, age range: 49 to 69 years-old (mean 58.7 years-old). Almost all patients commented on some degree of skin contraction and improvement in facial and neck contours immediately post procedure. At follow-up (4 – 20 weeks), 75% of patients continue to report a high degree of satisfaction. 95% of patients found the procedure tolerable requiring only topical anaesthesia and chilled air (Cryojet) for pain control during treatment. None required oral or injectable anaesthesia and only one third of patients requested additional inhaled nitrous oxide. 85% of patients would consider having the Ultraformer 3 again in the future and 75% would recommend the procedure to a friend. The patient satisfaction survey is summarized in table 1. Two blinded dermatologists were asked to study a series of subject images consisting of baseline images, immediately post-procedure images and one or more follow-up images ranging from 4- to 20- weeks post-procedure (figures 1-4). The blinded dermatologists were then asked to pick out the 'best' (most improved) image, which correlated with the follow-up images in 71.4% of cases (5 out of 7 patients). The blinded dermatologists (D1 and D2) were also asked to pick out the 'worse' image, which correlated with the pre-procedure baseline images in 72.5% of cases. The blinded dermatologists' survey is summarised in table 2.There were no long term adverse events noted. Mild to moderate transient erythema is commonly seen post-procedure lasting approximately 30 minutes. One patient on fish oil developed mild bruising that resolved fully after a few days. There were 2 transient but notable post-treatment effects: one patient had transient

| Strongly Disagree (-2) | Disagree (-1) | Uncertain (0) | Agree (1) | Strongly Agree (2) | Weighted Mean (-2 to 2) | Median Score |
|---|---|---|---|---|---|---|
| Q1. I am satisfied with the outcome of the procedure | | | | | | |
| 0 respondents | 1 respondent | 4 respondents | 7 respondents | 8 respondents | 1.1 | Strongly Agree |
| Q2. I would consider having the procedure again in the future | | | | | | |
| 0 respondents | 0 respondents | 3 respondents | 7 respondents | 10 respondents | 1.35 | Strongly Agree |
| Q3. I would recommend this procedure to a friend | | | | | | |
| 0 respondents | 0 respondents | 5 respondents | 6 respondents | 9 respondents | 1.2 | Strongly Agree |
| 4. I find the comfort level of the procedure to be | | | | | | |
| 'very uncomfortable' 1 respondent | 'uncomfortable but bearable' 7 respondent | 'slightly uncomfortable' 7 respondent | 'comfortable' 4 respondent | 'very comfortable' 1 respondent | -0.15 | Slightly uncomfortable but bearable |
| Q5. I find the duration of treatment | | | | | | |
| 'much longer than expected' 0 respondent | 'longer than expected' 1 respondent | 'about right' 14 respondent | 'shorter than expected' 3 respondent | 'much shorter than expected' 2 respondent | 0.3 | About right |

**Table 1** Ultraformer patient satisfaction survey.

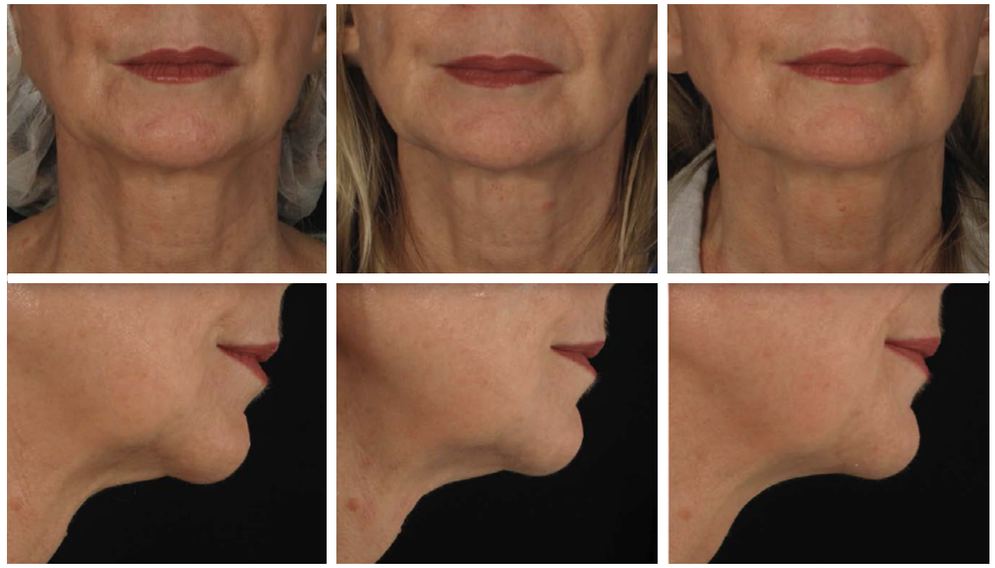

**Figure 1** 59 year-old female at baseline, 1-month, 2-months post-procedure (left to right).

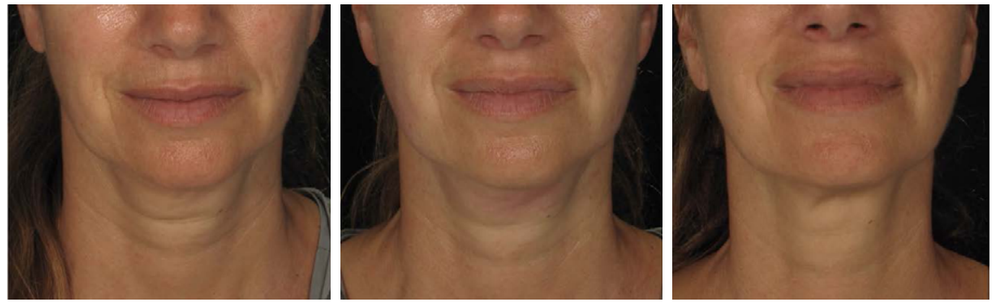

**Figure 2** 50 year-old female at baseline, immediately post, and 3-months post procedure (left to right).

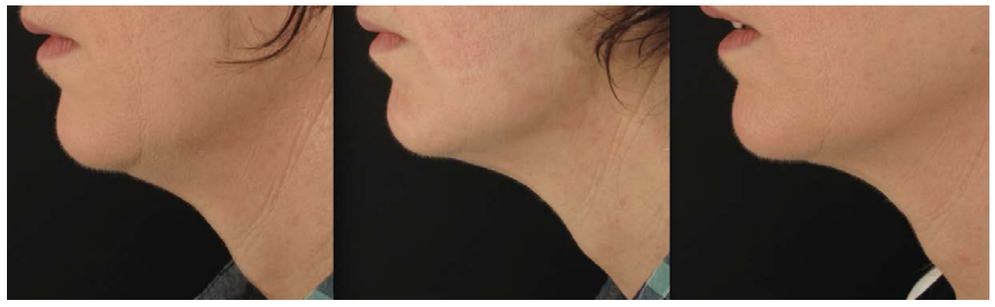

**Figure 3** 50-year old female at baseline, immediately post, and 3-months post-procedure (left to right).

| Case | Post (Week) | D1 * 'worse' | D2 * 'worse' | D1 ** 'best' | D2 ** 'best' |
|---|---|---|---|---|---|
| 1 | 0, 6, 20 | 0 | 0 | 1 | 0 |
| 2 | 0, 10 | 1 | 1 | 1 | 1 |
| 3 | 0, 4 | 0 | 1 | 0 | 1 |
| 4 | 0, 4 | 1 | 1 | 0 | 1 |
| 5 | 0, 6 | 1 | 0 | 1 | 0 |
| 6 | 0, 4, 8 | 1 | 0 | 1 | 1 |
| 19 | 0, 8 | 1 | 1 | 1 | 1 |
| 7 | 0 | 0 | 1 | | |
| 8 | 0 | 1 | 1 | | |
| 9 | 0 | 1 | 1 | | |
| 10 | 0 | 1 | 1 | | |
| 11 | 0 | 0 | 0 | | |
| 12 | 0 | 0 | 0 | | |
| 13 | 0 | 1 | 1 | | |
| 14 | 0 | 1 | 1 | | |
| 15 | 0 | 1 | 1 | | |
| 16 | 0 | 0 | 1 | | |
| 17 | 0 | 1 | 1 | | |
| 18 | 0 | 1 | 1 | | |
| 20 | 0 | 1 | 1 | | |
| | | 14/20 * | 15/20 * | 5/7 ** | 5/7 ** |

* correctly identifies the baseline ('worse') picture. D1, D2 mean = 72.5%
** correctly identifies the best ('lasest') picture. D1, D2 mean = 71.4%

**Table 2** Blinded physician (dermatologists D1 and D2) survey.

mild linear erythematous plaques for 24 hours after treatment and another patient had subtle asymmetry of smile for a few days after treatment, which fully resolved after one week.

## DISCUSSION

MFU has been used for skin tightening in facial and non-facial sites.[5,6,9,10] Upper face tightening for brow and eyelid laxity are easier to objectively measure using fixed landmarks such as pupils and eyebrows and have been subjected to studies with various skin tightening procedures including MFU.[6] The jowl and neck areas are more difficult to consistently measure in the absence of an objective grading scale or readily identifiable landmark and studies have to rely on photographic changes and subjective patient self-assessment. We elected to study jowl and neck tightening because this is an area that is not easily treatable by other non-invasive techniques such as cosmetic injectables and non-MFU skin tightening procedures. The aging jowl and neck is therefore of great concern to all cosmetic patients, with progressive lagging in these areas with the passage of time, relative to the mid to upper face, resulting in strong patient demand in our practice for jowl and neck tightening procedures.

The limitations of skin tightening devices include inconsistent results, need for multiple treatments, procedural discomfort, durability of results and costs.[5] Patient satisfaction rate for skin tightening procedures range from 31% for monopolar radiofrequency to 80% for MFU.[8,11] In our study, 75% of patients are satisfied with the treatment outcome and this high patient satisfaction rate in part translates to a desire for repeat procedures (85%) and referring the procedure to others (75%). Procedural tolerability is another important patient consideration for return visits. In this regard, Ultraformer 3 is notably different from non-Ultraformer MFU in that it is well tolerated - 95% reported the experience as either ‘very comfortable’, ‘comfortable’ or ‘slightly uncomfortable but bearable’. The average treatment time is less than 20 minutes and 70% of patients rated the treatment time to be ‘about right’ while another 25% rated the treatment time to be ‘shorter’ or ‘much shorter’ than expected. Pre-Ultraformer devices tend to be associated with a significant discomfort requiring oral anxiolytics and oral / intramuscular narcotic analgesics and is clearly a significant barrier to the uptake of pre-Ultraformer MFU treatments.[4]

The safety of MFU is well established with a very low reported incidence of adverse events. Overheating of the skin with inappropriately high energy settings can result in blisters and reticulate scars but the associated pain will usually prevent this from happening and indeed there are no reports of MFU related scarring.[4] In our study, there were 2 transient post-treatment effects that deserve further comment: firstly, transient mild linear erythematous plaques can occur but these generally last for less than 24 hours although there has been report of these lasting for days with subsequent full resolution with topical steroids. When linear plaques become noticeable during treatment, a decrease in fluence is recommended. Another patient had transient thermal neuropraxia from inadvertent MFU targeting of the left marginal mandibular nerve resulting in subtle transient lip weakness. The temporal nerve and marginal mandibular nerve are vulnerable to MFU effects at the temple and lateral chin respectively, and are ‘caution areas’ during MFU therapy. Transient sensory thermal neuropraxia presenting as tingling and numbness can also uncommonly occur.

Blinded physician assessment of the before-and-after photos show a noticeable change post-procedure (1- to 4.5- months, mean: 8.6 weeks). Although there is an initial non-response rate of up to 27.5%, based on on blinded 2-dimensional photo-ratings, these ‘non-responders’ may subsequently show a noticeable tightening response at a later time-point (figure 4), consistent with delayed collagen remodeling effects.

The durability of results has not been well studied and there is no data on the effects of regular MFU treatment on skin ageing. Although MFU is generally considered a single session treatment, others have anecdotally observed better patient results with up to 3 treatment sessions at 4-6 month intervals, followed by annual maintenance sessions (personal communication, Korea). We hypothesize that regular maintenance MFU treatments may slow down skin laxity and aging and we will examine this with longitudinal data on the effect of regular MFU on skin laxity over time. Our commercial experience with Ultraformer 3 has been very favourable. There is a market gap for a non-surgical lower face and neck tightening procedure that delivers consistent results without being too uncomfortable or protracted. Patients are often very receptive to procedural recommendation for jowls and facial sagging and will be prepared to have repeat treatments and recommend the procedure to others if the procedure meets their expectation in efficacy and tolerability. From the practitioner’s perspective, the Ultraformer 3 is easy to handle and drive and can be performed by doctors, nurses, dermal therapists and other trained allied health practitioners. Ultraformer 3 can be delegated to suitably trained staff because of its dependable, non-laser technology coupled with a low incidence of adverse events. The device affordability and low running cost makes it an attractive business and commercial proposition, which adds value for the patient. The limitations of this study are a relatively small sample size, a relatively short follow-up period of less than 6-months and potential investigator bias from using an industry-sponsored device (Cryomed Australia).

## CONCLUSION

MFU therapy with the Ultraformer 3 is a safe, effective high-speed, low-pain procedure that meets a clear

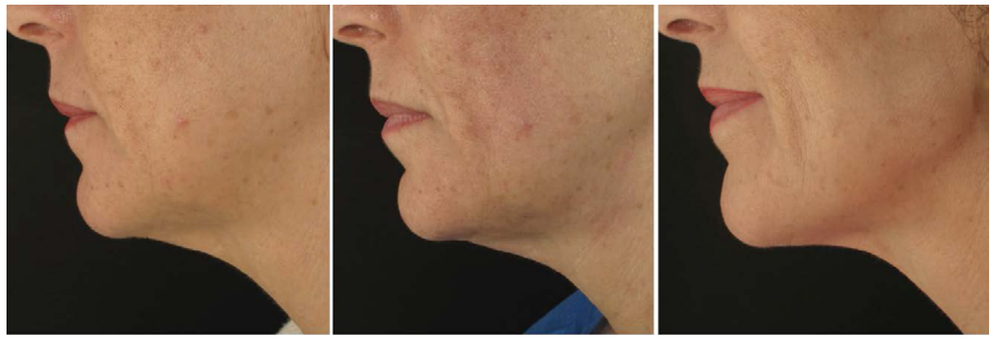

**Figure 4.** 50 year-old female at baseline, immediately post- and 1-month post-procedure (left to right) highlighting gradual neck and jawline tightening even though there was no observable change immediately post-procedure (centre image).

need amongst patients seeking skin tightening. The procedure induces noticeable skin tightening post-procedure with a 75% patient satisfaction rate that is independently and objectively verifiable. Patients tolerated the procedure well with only topical anaesthesia and chilled air cooling. The favourable procedural experience and results convert to an 85% reported desire for repeat procedures and 75% referral rate to others.

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# Face Lifting and Body Modeling without a Scalpel

Radosław Rzepnikowski

## Face Lifting and Body Modeling without a Scalpel

Radoslaw Rzepnikowski, MD | Poland

Ultraformer III is an innovative device used in the field of aesthetic medicine for facelift and body modeling and face without scalpel. Thanks to HIFU technology, the skin of the body is firmly nourished and rejuvenated. HIGH means High Intensity Focused Ultrasound is a technology that uses a focused ultrasonic wave that is responsible for heating the tissues of the skin, muscles and fat, which in turn leads to their shrinking and micro-stimulation stimulating the formation of new collagen.

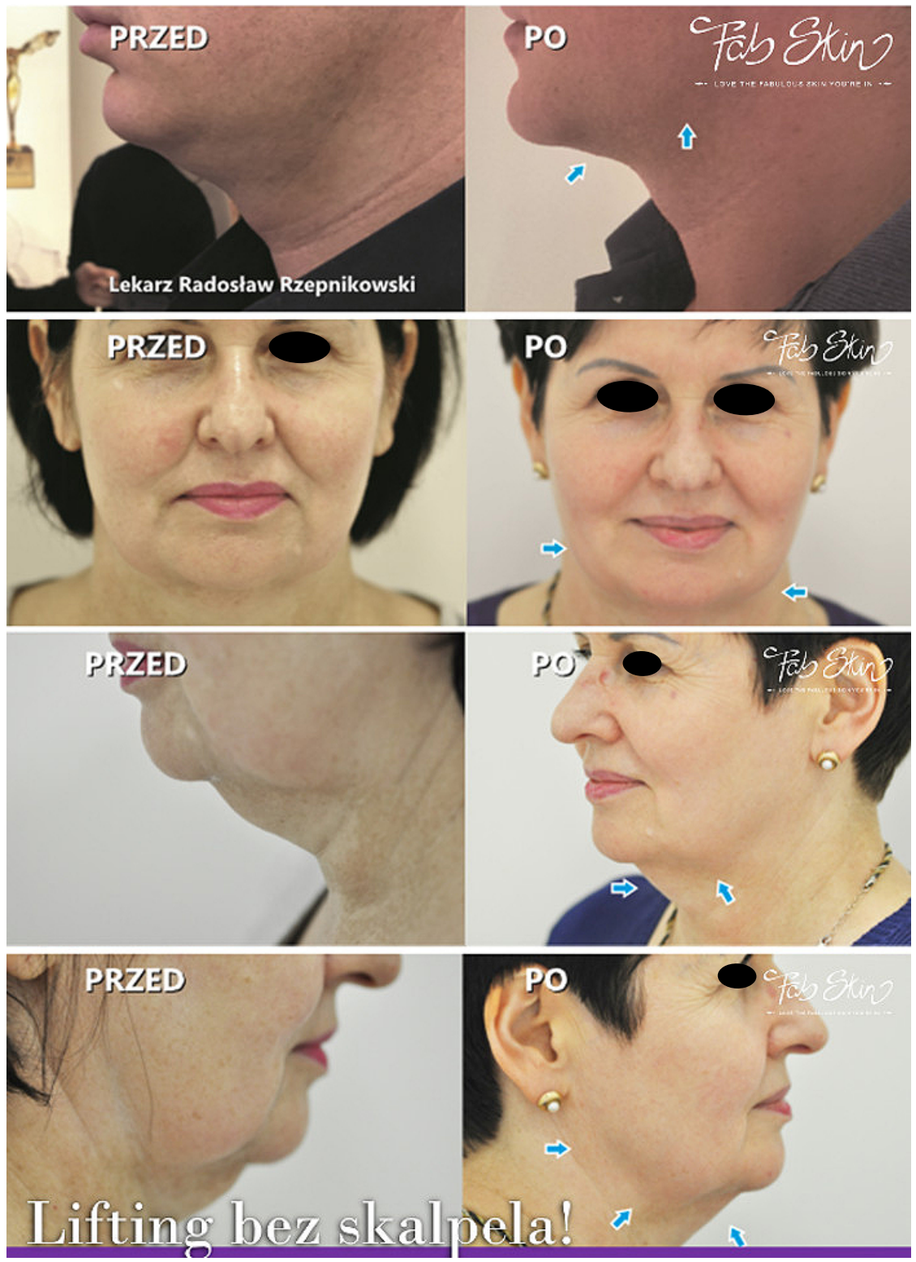
The Ultraformer III machine, which allows for a non-operative lifting, is a milestone in the treatment of skin pruritis, especially in the most sensitive areas such as breast, buttocks, abdomen, thighs and shoulders . The ultrasound method is safe, noninvasive, clinically tested and above all effective. It gives spectacular results that satisfy every patient. After just one treatment the skin becomes more elastic and taut.

The non-invasive Ultraformer III machine is an incredible American equipment for skin lifting without the use of a scalpel. This is the latest aesthetic medicine solution utilizing a highly concentrated ultrasound beam to penetrate deeply into the tissues, allowing for the non-operative facelift of the body and face. One of its many advantages is the ability to perform surgery on any part of the body.

During the modeling process, a special head emitting ultrasonic waves is applied to the selected area of the patient's body that penetrates into the tissue. The heated tissues shrink, resulting in tension and increased skin tension. Skin smoothes, tightens, firms - giving spectacular effects like lifting. Ultraformer helps effectively eliminate slack, unsightly skin from places such as the abdomen, thighs, shoulders, neckline, neck.

The Ultraformer III has transducers of varying penetration depths ranging from 1.5 to 9 mm and therefore adapt to any skin type and age. Accurate power regulation makes the treatment perfectly suited to the conditions and needs of the patient.

# ULTRAFORMER III



SMAS Face Lift with HIFU technology (High Intensity Focused Ultrasound) for the ULTRAFORMER Unit

Klaus FRITZ

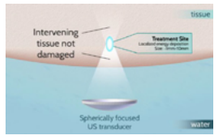
# SMAS Face Lift with HIFU Technology (High Intensity Focused Ultrasound) for the ULTRAFORMER Unit

Klaus Fritz, MD I Germany

Speech at IECTC (International Educational Course-Training for Cosmetologists)
Dermatology
President German Academy of Dermatology (DDA)
Past President ESLD (European Society of Laserdermatology)
Lecturer and Consultant at University Osnabrueck(D)
AssociatUniv.-Professor at University of Medicine and Pharmacy Carol Davila (Ro)

## BACKGROUND

As human gets older, skin and it's under structural tissues constantly get ageing process. Typically, number of fibroblast on the skin decreases and collagen synthesis also decreases and functions and numbers of many skin appendages are also dropped.
In the past, ablative laser or chemical peeling was used for face lifting. Recently, HIFU was introduced as a new treatment modality for skin tightening and rejuvenation.
HIFU (High Intensity Focused Ultrasound)
The deposition of acoustic energy can cause different bio-effects, such as transiently increasing cell and vessel permeability, tissue heating and irreversible tissue destruction.




Achieving Non-invasive lifting procedure, temperature is critical factor. Micro-focused ultrasound heats tissue to >60°C, to denature collagen and cause contraction of the collagen structure without damage surrounding area.

## INTRODUCTION

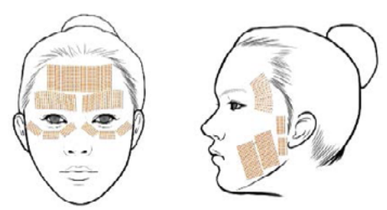
Face and scalp are composed of several layers and these can be specifically composed into five standard layers: Skin, Subcutaneous layer, Musculoaponeurotic layer (SMAS: Superficial Muscular Aponeurotic System), Loose areolar tissue (spaces and retaining ligaments), fixed periosteum and deep fascia.
For the face lifting effect, target tissue is dermis, connective tissue in fat layer and SMAS (at a depth of 4.5mm beneath the skin. The HIFU (High Intensity Focused Ultrasound) is irradiated fractionally at a depth of 3.0 or 4.5mm). The SMAS at a depth of 4.5mm is coagulated by the focused beams of light (fascia, SMAS, fibrous tissue). Skin regeneration and lifting effect by newly formed collagen and elastin.
Focused ultrasound heat up 65~70 (only focal area) and coagulate the tissue at the target lifting-4.5mm, 3.0mm and 1.5mm depth.

## METHOD

The best indications for face contouring are Forehead wrinkles, eyebrow, check, Jowl line, wrinkle lifting, skin tone improvement, V-line forming, double chin and neck wrinkle.
Focused ultrasound heat up 65~70°C (only focal area) and coagulate the tissue at the target lifting-4.5mm, 3.0mm, 2.0mm and 1.5mm depth standard treatment segments are as below. SIDE EFFECTS
The skin might appear flushed at first and the redness should disappear within a few hours factors affecting treatment response.

## CONCLUSION

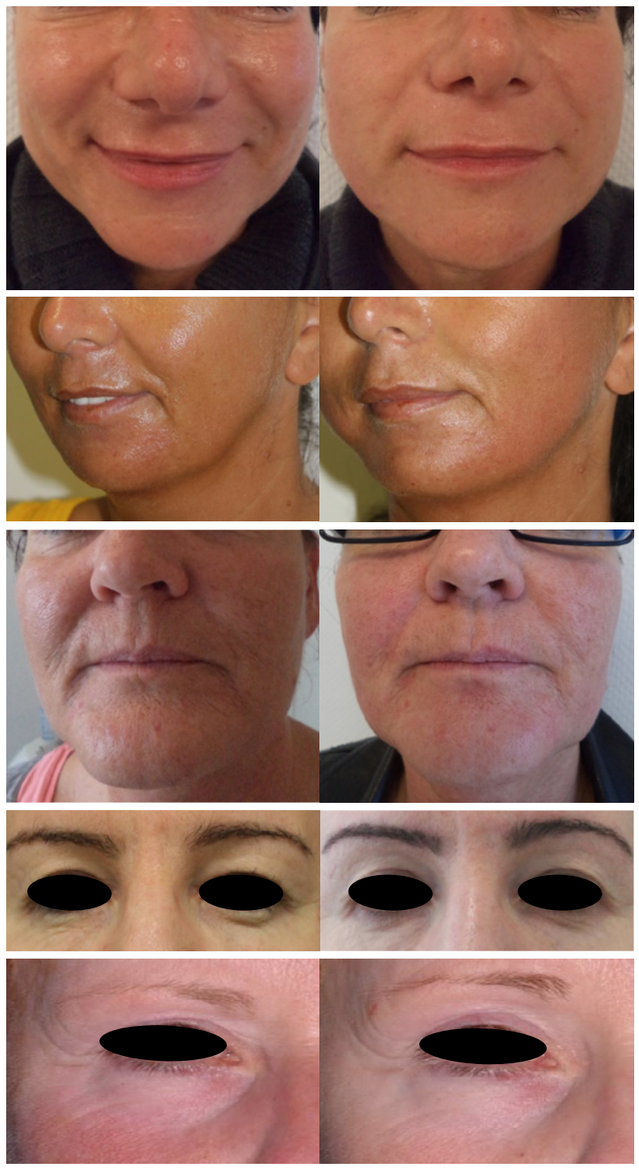
There will always be patients who are candidates for surgery but just don't want to go under the knife. HIFU treatment will not provide them drastic results like face lifting surgery. However, it is the only non-invasive procedure which reaches the same layers of skin as are addressed in a surgical facelift. There are some factors affecting HIFU treatment response; skin laxity- amount



| | Treatment Cartridge |
|---|---|
| Forehead | 1.5mm |
| Around eyes | 1.5mm |
| Cheek | 3.0mm/4.5mm |
| Lateral neck | 3.0mm/4.5mm |
| Submentum | 3.0mm/4.5mm |

of excess, loose skin on the face or neck, Volume: Degree and distribution of fat on the face, Skin quality: extent of lines, wrinkles, crepiness and sun damage. And Age and the lifestyle/health (smoker or nonsmoker, underlying heath issues) can be the factors as well.

HIFU treatment creates new collagen at multiple depths within the skin for a more multi-dimensional approach. Patients will likely need more than one treatment to get the results and will keep them coming back every 1~2 years for continued maintenance.



# The Most Exciting International Evolution in the Non-surgical Facelift

Serena Lim, MD

## The Most Exciting International Evolution in the Non-surgical Facelift

Serena Lim, MD I Australia

Hailed as the ‘next evolution’ in aesthetic science, the Ultraformer has taken the anti-ageing world by storm by performing the same procedure as cosmetic surgeons – but without cutting or disrupting the skin.

Necks, eyelids, chins, jawlines, brows and areas of the body that are wrinkling or sagging, such as armpits, stomachs, thighs, will lift under the ultrasound technology of the Ultraformer. And the bonus is that it can be performed over 30 minutes in a lunchtime break with no down-time, minimal side-effects and is almost completely pain free.

"Turkey necks, droopy eyelids, lowered brow lines, surface pores, even flabby arms and thighs: these are all areas the Ultraformer treats with immediate and ongoing results,” says Dr. Serene Lim. "Plastic surgeons in Europe are raving about this treatment due to the results in face and body contouring and tightening."

After years of research and working in the industry, Dr. Serene has long steered away from treatments in facial rejuvenation that have possible side-effects. So Ultraformer ticks all the boxes and is an affordable and less-frequent alternative to many procedures on the market.

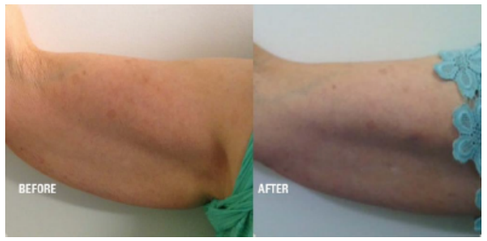
"It is very precise, so the fat layer of the skin can be spared and fat necrosis avoided. All other modalities in facial rejuvenation treat the surface of the skin to the deep layers, so there is potential for more wrinkle formation when fat is destroyed, and pain when the nerve-rich dermis is affected. That won’t happen with the Ultraformer, and it is almost pain-free," she says.

The treatment takes about 30 minutes and is completely safe. It works through the ultrasound, which has been used in medicine for more than 70 years, contracting and shortening muscle fibres, which causes the lifting effect, stimulating collagen for a plumping youthful appearance or reducing fat for stubborn fatty deposits like under the chin.

"I am always after a natural face and one that can be achieved with minimal side-effects (some people may experience short term redness and/or tenderness). Ultraformer ticks all the boxes for me.

It’s a really exciting treatment in the facial rejuvenation area and my clients are more than happy with the results we are achieving," says Dr Serene.

The Ultraformer is the only treatment on the international market that works on the muscle fascia (SMAS) deep below the skin, which is the area surgeons tighten for face and neck lifts. Rather than using a needle or knife, the Ultraformer harnesses ultrasound technology to radiate energy to this layer to tighten and lift.

# ULTRAFORMER Achieves Effective Non-surgical Face Lifting, Tightening and Whitening

Klaus Fritz I Franco Lauro I Beom-Joon Kim

## ULTRAFORMER Achieves Effective Non-surgical Face Lifting, Tightening, and Whitening

Klaus Fritz et al. I Germany, Italy & South Korea

Klaus Fritz, M.D.
Director
Dermatology and Laser Centers Landau, Germany
Lecturer
University of Osnabrueck
Germany

Franco Lauro, M.D.
Plastic Surgeon
Private Practice
Bologna, Italy

Beom-Joon Kim, M.D., Ph.D.
Department of Dermatology
College of Medicine
Chung-Ang University
Seou l, Korea

Ever since its recent entrance in the aesthetic market, the Ultraformer device from Classys, Inc. globally continues to impress physicians and their patients with excellent face and neck lifting treatment outcomes. This innovative device offers cosmetic patients a variable non-invasive option to more traditional surgical lifting and tightening treatment approaches.

"In my opinion, the Ultraformer device is going to have a significant impact in the aesthetic industry," said Klaus Fritz, M.D., director of the Dermatology and Laser Centers in Landau, Germany, lecturer at the University of Osnabrueck, Germany, and former president of the European Society of Laser Dermatology. "The treatment outcomes one can achieve for face lifting and skin tightening with this device are remarkable:'

Based on mature, time-tested High Intensity Focused Ultrasound (HIFU) technology, Ultraformer effectively treats the superficial and deeper dermis, as well as the superficial muscular aponeurotic system (SMAS) with a triple layer lifting effect. Heating the targeted area to between 65 and 75°C, the highly focused acoustic energy creates thermal coagulation zones at 1.5mm, 3.0mm and 4.5mm depths, optimally penetrating the skin with geometric precision, while completely sparing the epidermis.

"HIFU affects all three layers of the superficial and mid-dermis as well as the SMAS, a method that may be more effective than one-pass protocols for skin tightening," said Beom Joon Kim, M.D., ph.D,. a professor in the department of dermatology, at the College of Medicine, Chung-Ang University, Seoul, Korea.

Certified by the Korean FDA for eyebrow lifting and CE marked, Ultraformer can also achieve excellent aesthetic outcomes in molar augmenting jowl lifting, nasolabial fold reduction and periorbital wrinkle reduction, as well as overall skin tightening and rejuvenation in targeted areas. "In my experience, the speed and simplicity of the treatment, coupled with the excellent cosmetic results one can achieve, distinguish the Ultraformer device from any other laser treatments employed for the same indications;'

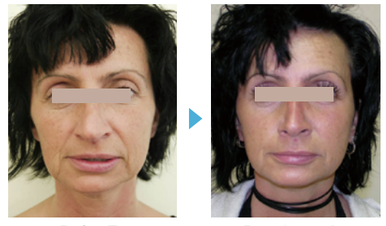
Dr.Fritz stated.

Collagen is the primary protein in the dermis, along with subcutaneous fat and the SMAS. It is a family of structural proteins responsible for the strength and resilience of the skin and other tissues. HIFU energy heats the collagen fibers leading to denaturation. This in turn results in a thickening and shortening of the collagen fibers, greater tissue tension due to the rubber elastic properties of collagen, and ultimately, tissue tightening.

Soon after an Ultraformer treatment session, patients will appreciate a firmer feel to the skin, along with a smoothening of fine lines. While this immediate plumping effect is temporary, it signals the initiation of the neocollagenesis process."Following the initial effects, a wound healing response is initiated in the skin, resulting in the formation of new collagen fibers, which provides tightening of the skin in a longer term.

Photo courtesy by Dr. Franco Lauro

BeforeTx Post 2 months



BeforeTx Post 2 months

After four weeks of treatment, patients' facial contours and fine wrinkles show significant improvement. Additional skin firming and tightening has shown over the next two to three months after treatment," Dr. Kim reported. This non-invasive procedure is associated with no downtime, allowing patients to return to daily activities immediately after the treatment, and dramatic results can be achieved as well with improvements seen in facial skin tightening and fine wrinkles up to six months after. Maintenance treatments could then be performed at three or six month intervals, depending on the degree of lifting and tightening that needs to be addressed in the individual patient at baseline.

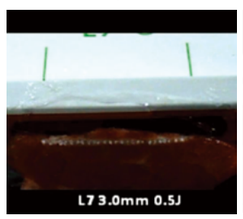
"In my experience, the Ultraformer is the best device I have ever used for soft tissue and skin tightening;' said Franco Lauro, M.D., a plastic surgeon in private practice in Bologna, Italy. Treatments are extremely quick, with a typical face and neck tightening procedure lasting approximately 20 minutes, allowing patients to quickly return to their daily routine."

According to Dr. Lauro, there is no downtime associated with the Ultrafomer procedure and to date, he has not seen any complications from treatment underscoring the device's safety. "Using the Ultraformer, I can easily and safely treat every part of the body, and all Fitzpatrick skin types without hesitation, he added, "we can even combine treatment with other complementary aesthetic procedures in the same session."

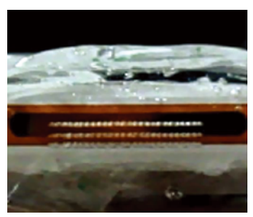
Featuring dual handpiece, the Ultraformer device offers a fluence of 0.1 to 1 J, and is equipped with three different cartridges ideal for the triple layer HIFU treatment approach, namely L7-3: 7 Mhz(3 mm), L4-4.5: 4 Mhz(4.Smm), and L?-1.5:7 Mhz(l.5 mm). Beyond its benefits in skin tightening, as well as face and neck lifting, the Ultraformer device has also shown its effectiveness in lightening skin, further demonstrating its versatility in cosmetic treatments. Dr. Kim, who is also a professor at the R&D Center of the Chung-Ang University Hospital-appointed by The Ministry of Education of the Republic of Korea for the Vrain Korea 21 Plus project team in the arena of dermatological science (2013-2020) - has explored the Ultraformer's effectiveness for this indication.

"I have performed NB-UVB examinations for the treatment of pigmentation in brown guinea pigs. From our research, my team and I have observed significant changes in skin pigmentation and can confirm the Ultraformer's efficacy in lightening the skin of animal models. We emitted both 0.1 J and 0.2J of the device's L7-1.5 settings in the study. Using these parameters, the lightening effect was observed three weeks following a protocol of four treatments per week for a month period." Dr. Kim® reported.

Numbers of melanin have been reduced after Ultraformer treatmeant by 7Mhz 1.5mm depth at 0.2J. The results were observed by Fontana Masson Stain, Image Pro Analysis and Folliscope as following picture of [1 ] [2] [3].




[ MeatTest ]



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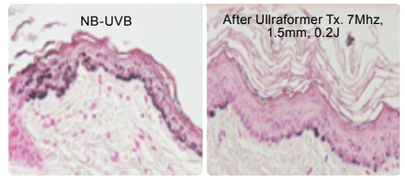
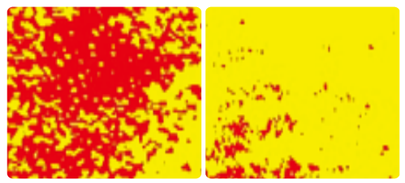
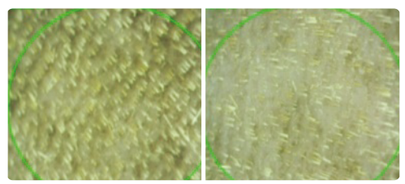



[1] Fontana Masson Stain



[2] Image Pro Analysis



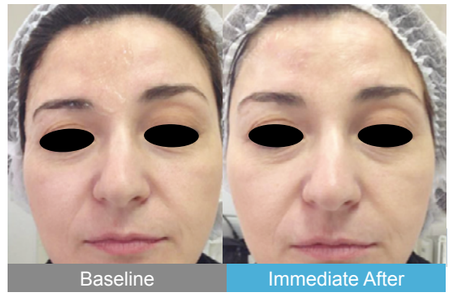
[3] Folliscope

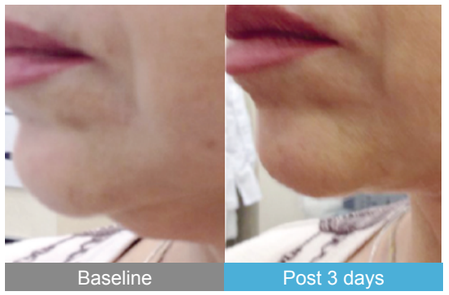
® Dr. Beam June Kim, professor at R&D Center of the Chung-Ang University Appointed by The Ministry of Education of the Republic of Korea for the Brain Korea 21 Plus project team 1n the arena of dermatology science (2013-2020)



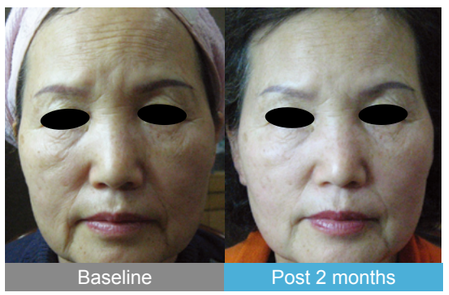
**Face & Neck lifting immediate and post few days**



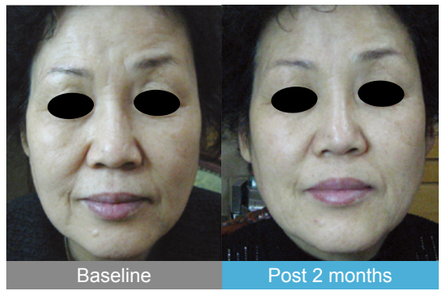


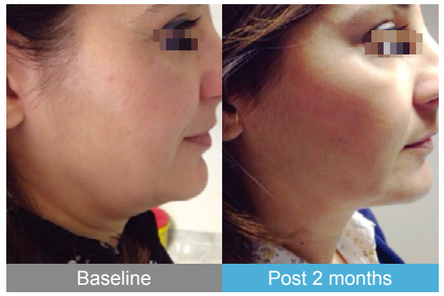

**Results post 2 month**

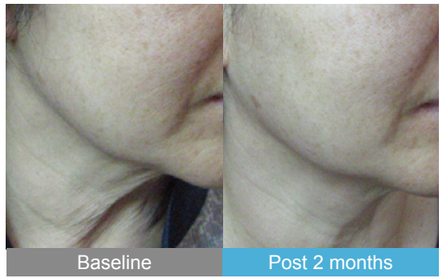



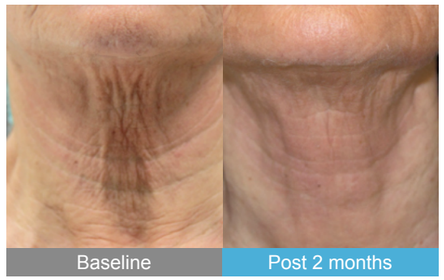


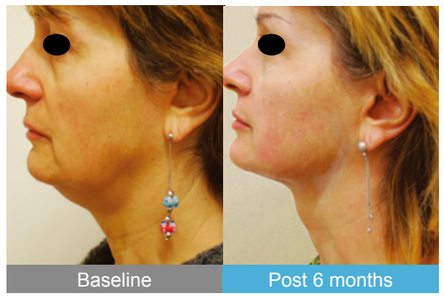





**Results post 6 month and 12 month**




# Evaluation of Micro Focused Ultrasound for Lifting and Tightening the Face

In Ho Lee | Seung Min Nam | Eun Soo Park | Yong Bae Kim

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## Evaluation of Micro-focused Ultrasound for Lifting and Tightening the Face

In Ho Lee et al. | South Korea

Background Micro-focused ultrasound (MFU) has developed as an effective, noninvasive, skin-tightening method. However, certain factors have limited its replacement of invasive surgical procedures, including a relative lack of efficacy, persistence, and reliability. The purpose of this study was to evaluate the efficacy and safety of MFU for noninvasive skin tightening and to determine how long the skin tightening can be maintained.

Methods Between October 2013 and November 2014, 41 patients with sagging and laxity of the facial skin were treated with MFU. The treatment was performed following the manufacturer's recommended protocol that called for 300 treatment lines. We evaluated the patients using an automatic skin diagnosis system at pretreatment, and 2 and 4 months after treatment.

Results Of the 41 patients treated using MFU, 3 patients were lost to follow-up for nonstudy-related reasons. In our study, 38 patients (1 male and 37 female) were evaluated and ranged in age from 37 to 52 years. The median skin grade scores were 5 at pre-treatment, 3 at 2 months post-treatment and 3 at 4 months post-treatment. After comparing pre-treatment and 2 months post-treatment, pre-treatment and 4 months post-treatment, and both 2 and 4 months post-treatment, there were statistically significant differences ($P<0.01$).

Conclusions This study suggests that the aging face, with wrinkling and sagging, can be improved using MFU, while minimizing injury to the epidermis and dermis.

Keywords Micro-focused Ultrasound, Aging face, Lifting

### INTRODUCTION

The signs of aged facial skin are not only fine lines and surface irregularities, but also sagging and wrinkling [1]. Noninvasive skin tightening is superior to invasive or surgical skin tightening in terms of rapid return to work, short recovery time, and low risk of adverse events. Because of these advantages, patients who desire a skin-tightening procedure prefer noninvasive skin tightening to invasive or surgical skin tightening [1,2].

To meet the demand of patients for noninvasive skin tightening, numerous devices have been developed. Laser and radiofrequency devices have been developed to resolve skin wrinkling and sagging [1-8]. Recently, micro-focused ultrasound (MFU) was developed as an effective noninvasive skin-tightening method. MFU is able to heat tissue greater than 60°C and produce a small thermal coagulation zone (<1 mm3) to reach the mid- to deep reticular layers of the dermis and subdermis while minimizing overlying papillary dermal and epidermal injury [9-11]. The delivery of MFU to a targeted zone in the superficial musculoaponerotic system (SMAS) provokes immediate contracture of denatured collagen and the initiation of neocollagenesis and collagen remodeling [10,12]. This action of MFU provokes noninvasive skin tightening and lifting of sagging facial skin. Certain factors have limited its replacement of invasive surgical procedures, including a relative lack of efficacy, persistence, and reliability. The purpose of this study was to evaluate the efficacy and safety of MFU for noninvasive skin tightening and to determine how long the skin tightening can be maintained.

### METHODS

Between October 2013 and November 2014, 41 patients with sagging and laxity of the facial skin were treated

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*Correspondence: Seung Min Nam Department of Plastic and Reconstructive, Soonchunhyang University Bucheon Hospital, 170 Jomaruro, Wonmi-gu, Bucheon 420-767, Korea. E-mail: zodiac1003@naver.com*

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with MFU using 4-MHz, 4.5 mm and 7-MHz, 3.0 mm depth transducers (Ultraformer®, Classys Inc., Seoul, Korea). Treatment was performed following the manufacturer's recommended protocol that called for 300 treatment lines. Patients with active systemic or local infections, local skin diseases that might alter wound healing, history of psychiatric illness, and soft tissue augmentation material were excluded from this study.

**Pretreatment preparation**

Five percent lidocaine, as a topical anesthetic ointment (EMLA, AstraZeneca, Sdertlje, Sweden), was applied to the face for 45 minutes before the procedure. The ointment was washed off with mild soap and water immediately before the procedure.

**Ultrasound exposure protocol**

The ultrasound gel was applied to the skin. The transducer was placed firmly on the targeted skin surface and pressed uniformly for coupling to the skin. Treatment exposure was initiated (4-MHz, 4.5 mm depth transducers; 0.9 J/mm$^2$ and 7-MHz, 3.0 mm depth transducers; 0.8 J/mm$^2$), with a line of individual ultrasound pulses being delivered within approximately 2 seconds. Then, the transducer slid to the next location and was repositioned 3 to 5 mm laterally such that it was adjacent and parallel to the previous treatment line. Complete treatment of the face required 15 to 20 minutes.

**Post-treatment care**

The ultrasound gel was washed off. Patients experienced mild redness and swelling that could persist for several days. Patients were instructed to visit our hospital promptly if they encountered any other adverse effects.

**Table 1.** Patients Characteristics

| Characteristic | Value |
|---|---|
| Sex (Female, Male) | 37, 1 |
| Mean Age (range) | 46 (37-52) |

**Outcome evaluation**

We evaluated the patients using an automatic skin diagnosis system(A-One Lite®, BOMTECH Electronics Co., Seoul, Korea) at pretreatment, and 2 and 4 months after treatment. The automatic skin diagnosis system evaluated skin laxity using a scanner. The sagging and laxity of the skin were graded from 1 to 6 using the system. A high skin grade score means that the sagging and laxity of the skin are severe. The clinician examined the skin for evidence of edema, erythema, hypopigmentation, and hyperpigmentation after treatment.

**Statistical analysis**

Statistical analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). The Friedman test was used to compare the grade scores of patients at pretreatment, and 2 and 4 months after treatment. A P value less than 0.05 was considered statistically significant.

## RESULTS

All patients were treated using MFU and three patients were lost to follow-up for non-study related reasons. In our study, 38 patients (1 male and 37 female) were evaluated and ranged in age from 37 to 52 years (Table 1).

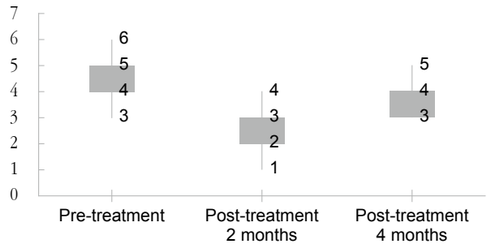


**Fig. 1**. Comparisons of skin grade scores at pre-treatment and 2 months post-treatment, pre-treatment and 4 months post-treatment 4 months, and 2 and 4 months post-treatment.

**Table 2.** The skin grade score

| Time | Pre-treatment (Median) | Post-treatment 2 months (Median) | Post-treatment 4 months (Median) | P-value*,†,‡ |
|---|---|---|---|---|
| Skin grade score | 5*,‡ (4-5) | 3*,† (2-3) | 3†,‡ (3-4) | < 0.01 |

*,†,‡P-value by Wilcoxon signed rank test.





Thirty-five patients immediately presented with slight erythema and edema after treatment, and three patients immediately presented with moderate erythema and edema after treatment. In all affected patients, both erythema and edema completely resolved by 2 days after treatment. Two patients presented with red linear striations of the check after treatment with the 3 mm transducer. They were treated using focal cooling without sequelae such as pigmentation and textural abnormalities. Hypopigmentation, hyperpigmentation, ulceration, and erosion were not present in any patients. There were no adverse events, such as nerve or muscle dysfunction, severe pain, bruising, and bleeding. The median skin grade scores were 5 (4-5) at pretreatment, 3 (2-3) at 2 months post-treatment, and 3 (3-4) at 4 months post-treatment (Fig. 1 and Table 2). After comparing pre-treatment and 2 months post-treatment, pre-treatment and 4 months post-treatment,

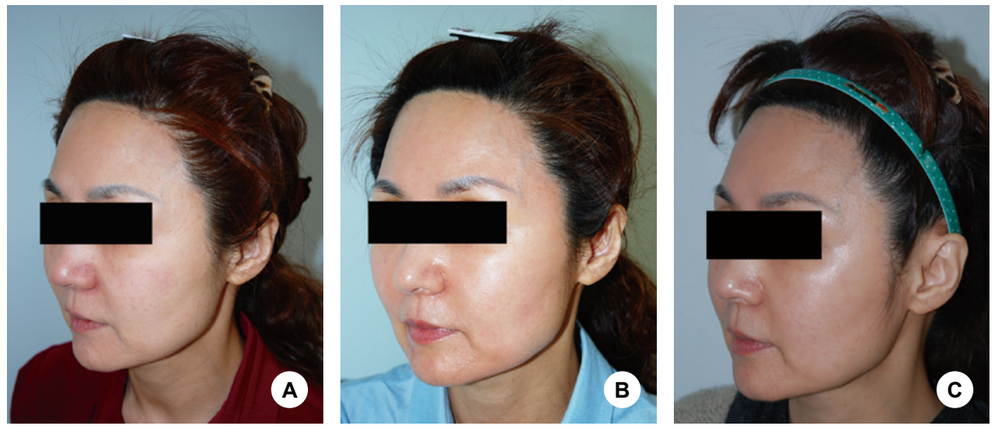


**Fig. 2.** A 46-year-old female patient with moderate skin sagging and wrinkling. At pre-treatment, she was examined by the automatic skin diagnosis system and was given a skin grade score of 5 (A). At 2 months post-treatment, the skin grade score was 2 (B). At 4 months post-treatment, the skin grade score was 4 (C).


**Fig. 3.** A 38-year-old female patient with moderate skin sagging and wrinkling. At pre-treatment, she was examined by the automatic skin diagnosis system and was given a skin grade score of 4 (A). At 2 months post-treatment, the skin grade score was 2 (B). At 4 months post-treatment, the skin grade score was 3 (C).

and both 2 and 4 months post-treatment, there was a statistically significant difference in skin grade score ($P<0.01$) (Fig. 2 and 3).

## DISCUSSION

The SMAS consists of viscous, elastic fibers and extracellular matrix [10,13,14]. It is associated with specific facial muscles, such as the platysma, orbicularis oculi, and levator labii superioris. Collagen within SMAS decreases 6% every decade [10]. This decrease in collagen contributes to a prominent nasolabial fold, and hooding of the brow and jowl [10,15,16]. To minimize post-treatment adverse events, clinicians have developed various non-ablative skin-tightening procedures to induce collagen shrinkage and remodeling [3,6,17]. Furthermore, ultrasound is able to penetrate into the subdermis layer and SMAS, and induce thermal coagulation to avoid undesired post-treatment adverse events compared with carbon-dioxide laser resurfacing [17-19].

Ultrasound energy has characteristics that are suitable for skin lifting and tightening. First, it is believed that ultrasound energy can be transmitted into the deeper subcutaneous layer of the face or even the SMAS, and is the most effective method for skin lifting and tightening [13,14,20-23]. Second, both the epidermis and dermis can be protected from ultrasound energy during its transmission, reducing the risk of advertent cutaneous layers [1].

Ultrasound used in medicine is classified into two types. One is high-intensity focused ultrasound (HIFU) and the other is MFU. HIFU uses high energy and is mainly used for nonsurgical ablation of tumors. HIFU can also be used to ablate adipose tissue for body contouring [10]. MFU uses much lower energy to treat the superficial layer of the skin [9] and is able to elevate the local temperature higher than 60°C to cause collagen contracture [24]. When energy is targeted to discrete areas within dermal and subdermal tissues, MFU induces discrete thermal coagulation zones while sparing adjacent non-target tissues [9,11,12,25]. In addition, the heat induces the denaturation and contraction of collagen fibers in the subcutaneous fat layer [26].

According to the results of our study, skin tightening at 2 and 4 months post-treatment was improved compared to pretreatment. However, skin tightening at 2 months post-treatment was better than at 4 months post-treatment, suggesting the efficacy of MFU gradually decreases treatment. Based on our results, we recommend that retreatment should be performed after 3 months for greater efficacy.

Our study had limitations. First, our study did not include patients who had severe skin sagging and wrinkling. We recommended the surgical face-lift procedure for these patients. Second, the post-treatment results were evaluated with an automatic skin diagnosis system, but the reliability of the system has not been established. Therefore, discrepancies may occur between the automatic skin diagnosis system and realistic skin conditions. Third, our study did not include any histologic evaluations. Fourth, the MFU device that we used in our study is not capable of clearly imaging the targeted facial anatomy. We cannot ensure proper acoustic coupling between the transducer and skin before the application of MFU energy. Despite these limitations, the results were evaluated objectively.

## CONCLUSION

This study suggests that the aging face, with wrinkling and sagging, can be improved using MFU, while minimizing injury to the epidermis and dermis. In addition, retreatment is recommended after 3 months to maintain the efficacy of the results.

## PATIENT CONSENT

Patients provided written consent for the use of their images.





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# Tightening Effects of High Intensity Focused Ultrasound on Body Skin and Subdermal Tissue: A Pilot Study

S.Y. Choi | Y.A. No | S.Y. Kim | B.J. Kim | M.N. Kim

DOI: 10.1111/jdv.13713 JEADV

Tightening Effects of High Intensity Focused Ultrasound on Body Skin and Subdermal Tissue: A Pilot Study

S.Y. Choi et al. | South Korea

S.Y. Choi,[1] Y.A. No,[1] S.Y. Kim,[2] B.J. Kim,[1],* M.N. Kim[1]

[1]Department of Dermatology, Chung-Ang University College of Medicine, Seoul, South Korea
[2]Department of Applied Statistics, Chung-Ang University, Seoul, South Korea
*Correspondence: B.J. Kim. E-mail: beomjoon@unitel.co.kr

**ABSTRACT**

Background High Intensity Focused Ultrasound (HIFU) has been introduced as a new treatment modality for skin tightening through application mainly to the face and neck.

Objectives This pilot study assessed the efficacy and safety of HIFU for body tightening in Asian females.

Methods Six Asian female adults were enrolled in this pilot study. All subjects were treated with HIFU to the both cheek, upper arm, lower abdomen, thigh and calf using the following probes: 7 MHz, 1.5 mm focal depth; 2 MHz, 3.0 mm focal depth; 2 MHz, 4.5 mm focal depth; 2 MHz, 6.0 mm focal depth and 2 MHz, 9.0 mm focal depth. Three blinded independent dermatologists assessed results using the Investigator Global Aesthetic Improvement Scale (GAIS) using paired pre- and post-treatment (week 4) standardized photographs. Also, we evaluated skin elasticity at all treated sites using a cutometer. Participants used the subject GAIS to assess their clinical improvement after treatment and rated their pain using a visual analogue scale (VAS) immediately, 1 and 4 weeks after treatment.

Results The three blinded evaluators judged all treated sites as showing clinical improvement 4 weeks after treatment. Skin elasticity measured via cutometer was significantly improved 4 weeks after treatment at all treated sites ($P < 0.05$). All patients scored themselves subjectively as more than 'improved' on the GAIS. Immediately after treatment the mean VAS score was 5.17  2.48, but no pain was reported at weeks 1 and 4. No permanent adverse effects were observed during the follow-up period.

Conclusion For body tightening, we applied HIFU using transducers with a lower frequency and deep focal depth to effectively deliver ultrasound energy to skin tissues. HIFU appears to be a safe and effective treatment modality for dermal and subdermal tightening.

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**CONFLICTS OF INTEREST**

None declared.

**FUNDING SOURCES**

None declared.

## INTRODUCTION

As skin tissue ages, its elasticity decreases and redundant facial, neck and body laxity are commonly seen. Various treatment modalities including surgical, laser and radiofrequency approaches have been used to improve skin laxity. Surgical lifting procedures for skin laxity are effective, but can leave visible surgical scars and are associated with risk and lengthy recovery times. Recently, patients seeking skin tightening are requesting safe and effective non-invasive alternatives associated with low risks and minimal downtime.

High Intensity Focused Ultrasound (HIFU) has been investigated as a tool for the treatment of solid benign and malignant tumours for the past several decades.[1] HIFU can produce small, micro-thermal lesions at precise depths in the dermis up to the fibromuscular layer, causing thermally induced contraction of collagen and tissue coagulation with subsequent collagenesis, while sparing the epidermis.[2–4] Recently, HIFU has been introduced as a new treatment modality for skin tightening and rejuvenation, primarily for the face and neck.[5] This pilot study was performed to assess the efficacy and safety of HIFU treatment for skin tightening treatment of body skin laxity in Asian females.

## PATIENTS AND METHODS

### Patients

This pilot study was approved by the Institutional Review Board of Chung-Ang University Hospital and followed the guidelines of the 1975 Declaration of Helsinki.

Based on the suggestion of a statistical committee, we referred to a previous study[6] to determine the number of subjects required for the current study. Six female adults were enrolled in the study.

**HIFU device**

The HIFU device used in this study was the ULTRAFORMER III, SHURINK (CLASSYS INC., Seoul, Korea). In this study, we used five different types of transducers. One of the transducers was a basic transducer for facial skin tightening (T1: 7 MHz, 1.5 mm focal depth). Four other transducers utilizing a lower frequency and deeper focal depths were newly developed for body skin tightening (T2: 2 MHz, 3.0 mm focal depth, T3:2 MHz, 4.5 mm focal depth, T4: 2 MHz, 6.0 mm focal depth and T5: 2 MHz, 9.0 mm focal depth). Each transducer delivered a series of ultrasound pulses along 25-mm long exposure lines. The pulse duration for each individual exposure ranged from 25 to 40 milliseconds.

**Treatment procedures**

Before treatment, we checked the patients, the thickness of skin components and all patients underwent treatment in five different areas including the both cheek, upper arm, lower abdomen, thigh and calf after topical anaesthetic cream. The sizes of the treated areas were 5.0 x 5.0 $cm^2$ on each cheek and 7.5 x 7.5 $cm^2$ on the lower abdomen as well as each upper arm, thigh and calf (Fig. 1).

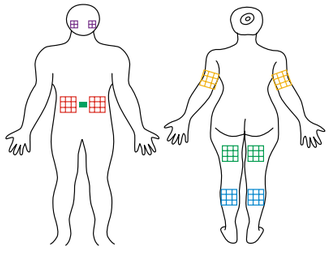

**Figure 1** Face and body treatment areas.

Ultrasound gel was applied to the treated skin and the transducer was pressed perpendicularly, uniformly and firmly to the skin surface. Treatment exposure was initiated with a line of individual ultrasound pulses being delivered over approximately 2s. Next, the probe was moved approximately 3 to 5 mm laterally so as to be parallel and adjacent to the line previously treated and the ultrasonic exposure was repeated.

Each side of the face was treated with three types of transducers (T1, T2 and T3), distributing a total of 552.5 J. Each side of the body was treated with five types of transducers (T1, T2, T3, T4 and T5), distributing a total of 817.2 J. We operated the powers with 1.0–1.5 J at each transducer. When patient feel pain, we reduced 0.1–0.3 J per time, but not increased up to 1.5 J. Complete HIFU treatment of the face and body occurred over 50–60 min. We prefer to use the shallow depth tips to deep depth tips. Because patient's pains are usually proportional to depth of tips.

**Efficacy and pain evaluation**

We evaluated the skin tightening effect of HIFU using photography and a cutometer. The investigator gathered digital photographs using identical cameras and camera settings (Canon EOS 600D, high-resolution setting, 5760 x 3840 pixels, Canon Inc., Tokyo, Japan) before and 4 weeks after the treatment. Three blinded independent dermatologists evaluated paired before and after photographs in a randomized fashion using the Investigator Global Aesthetic Improvement Scale (IGAIS). Subjects assessed the tightening effects using the Subject Global Aesthetic Improvement Scale (SGAIS) 4 weeks after treatment.

The Cutometer (Courage+Khazaka Electronic GmbH, Cologne, Germany) was used to measure skin elasticity. Among the cutometer-specific R values (R0–R9), we used the R7 value, which is defined as the ratio of elastic recovery to the total deformation and represents the biological elasticity. Pain was evaluated by visual analogue scale (VAS) immediately after week 0 and on weeks 1 and 4 after the application of HIFU. VAS is a simple and reproducible tool for the assessment of pain severity which consisted of 11 levels (0–10 points).

**Statistical analysis**

Statistical analyses were performed using SPSS version 18.0 for Windows (SPSS Inc., Chicago, IL). We used Hochberg step-up methods to adjust the values for multiple comparisons. Statistical comparisons between before and after treatments were performed using paired t tests. Data are presented as means  standard deviation. Ps < 0.05 were considered statistically significant.





## RESULTS

Six Asian female subjects (Fitzpatrick skin types III–V) with skin laxity were enrolled in this study. Their ages ranged from 43 to 54 years (mean ± SD: 48.17 ± 4.45 years) and showed similar skin depth. All subjects completed the HIFU treatments and follow-up for 4 weeks. The mean value of skin elasticity measured by cutometer was significantly increased at 4 weeks after treatment compared to baseline in all treated sites on the face and body (Fig. 2). The change in the mean value of skin elasticity measured by cutometer was greatest in the lower abdomen (Fig. 3). Three blinded independent dermatologists judged all patients as showing clinical improvement 4 weeks after treatment. In terms of cheek outcomes, 5 (83.3%) of 6 subjects were assessed as improved (IGAIS score 1), and 1 (16.7%) of 6 subjects as much improved (IGAIS score 2).

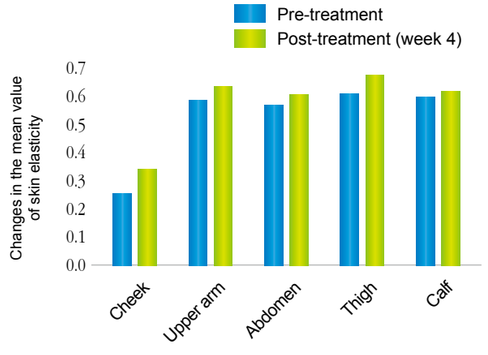


**Figure 2** Changes in the mean value of skin elasticity measured via cutometer (R7, mean  SD).

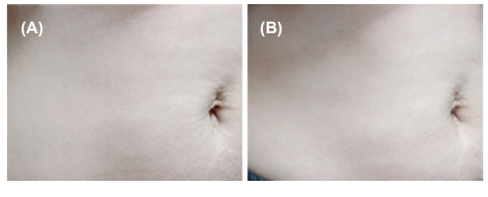


**Figure 3** The change in the skin elasticity in the lower abdomen (a) 0 week and (b) after 4 weeks.

In terms of body outcomes, including the upper arm, lower abdomen, thigh and calf, 6 (100%) of 6 subjects were assessed as improved (IGAIS score 1).

All subjects scored the SGAIS as more than score 1 in all treated sites. The mean SGIAS score in the calf was the highest. In the calf, 2 (33.3%) of 6 subjects were assessed as improved (SGAIS score 1), 2 (33.3%) of 6 subjects as much improved (SGAIS score 2) and 2 of (33.3%) 6 subjects as very much improved (SGAIS score 3).

We evaluated pain using the VAS immediately after treatment (week 0) and at weeks 1 and 4. Immediately after treatment, the mean VAS score was 5.17 ± 2.48 (range: 3–8). Three (50%) of six subjects rated their pain as mild, and 3 of (50%) 6 subjects rated their pain as moderate. One and 4 weeks after treatment, all subjects reported a VAS score of 0 (no pain).

One subject experienced edema on the right upper arm and one subject had muscle pain on the right calf after HIFU treatment. Both edema and muscle pain were mild and transient, and resolved within 1 week without any treatment. There were no serious or delayed adverse effects during the follow-up period.

## DISCUSSION

Recently, minimally invasive or non-invasive procedures have been gradually replacing surgical intervention in cosmetic dermatology. For the treatment of skin laxity, non-invasive, non-ablative thermal therapeutic devices can immediately denature collagen fibres and contract collagen fibres in the dermis and subcutaneous tissues and induce delayed neocollagenesis and elastogenesis.[7,8] Radiofrequency, infrared light sources and HIFU have shown clinical effects for skin tightening and rejuvenation on the face and neck. However, there have been fewer clinical trials or reports of skin and subdermal tightening effects of non-ablative thermal devices in sites on the body, compared to the face and neck.

In this pilot study, we sought to assess the efficacy and safety of HIFU treatments using transducers that were newly developed to be suitable for use on the body skin and subdermal tissue for the purpose of skin tightening in body laxity in Asian people. A previous clinical report on the effects of HIFU on tightening of

the periorbitum and body sites, which enrolled a total of 82 patients including 8 Asians, has been published. However, this previous clinical study used conventional HIFU transducers (10 MHz, 1.5 mm focal depth; 7 MHz, 3.0 mm focal depth and 4 MHz, 4.5 mm focal depth). We applied newly developed transducers to body sites with a lower frequency (2 MHz) and deeper focal depths (3.0–9.0 mm) compared with conventional transducers. Therefore, we expected that newly developed transducers could effectively deliver HIFU energy deeper into the skin and subdermal tissues of the body and show tightening effects and safety. Of course, it may effect to subcutaneous areas with 9.0 mm transducer. But it can reduce subcutaneous fats and lead to skin rejuvenation. Also, other reports said that if practitioner consider skin depths and regulate transducers well, 1.1–1.6 mm transducers are safe to use.[9]

Although we applied topical anaesthetic cream on treated sites, most subjects complained of a mild to moderate degree of pain during treatment in proportion to depth or power of transducers. Their pain subsided without the use of analgesics, but the injection of small amounts of local anaesthesia into the subcutaneous tissue should be considered for pain reduction.

In conclusion, HIFU treatment using transducers with a lower frequency and greater focal depth could be an effective and safe treatment modality for skin and subdermal tightening of the body. The limitations of this pilot study were the small number of subjects and the short-term follow-up period. Based on the results of this pilot study, well-designed controlled clinical studies with greater subject enrolment and long-term follow-up will be necessary to establish optimal treatment parameters.

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# ULTRAFORMER III

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