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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

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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 $10.5 \times 25.5\ mm^2$, 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.

TABLE 1 Treatment sessions and endpoints

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

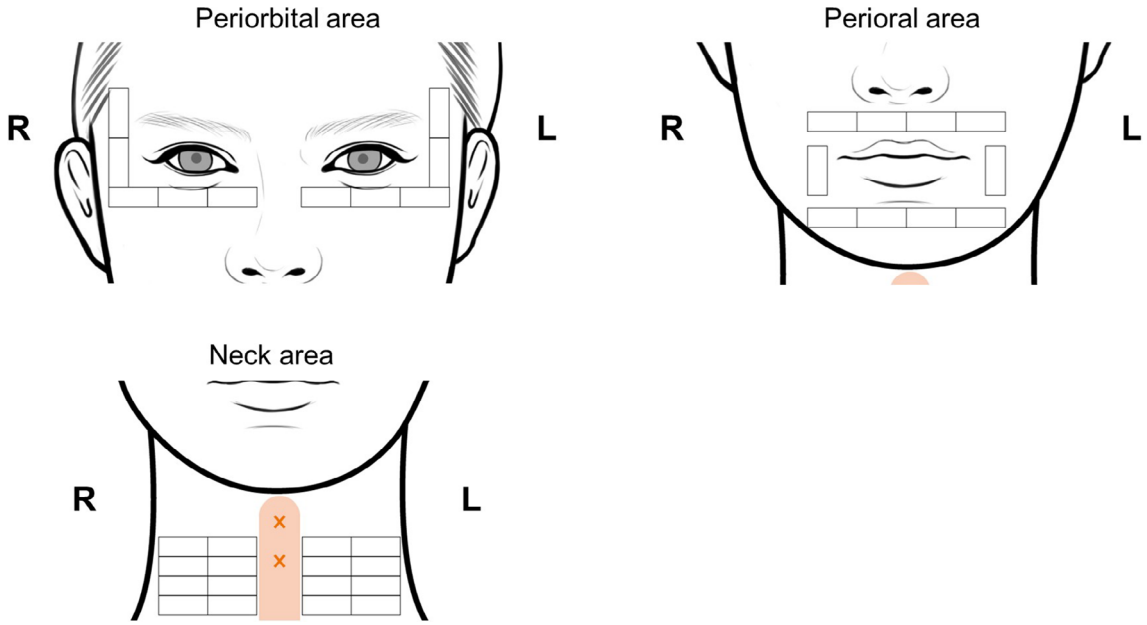


FIGURE 1 Treatment maps of the periorbital, perioral, and neck areas

TABLE 2 Explanations of efficacy assessments

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%)

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).

TABLE 3 Treatment results

Treatment				*N* (%)
Treatment per protocol—three times				100 (98.04)
	Energy (J)	Number of 1.05 × 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

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

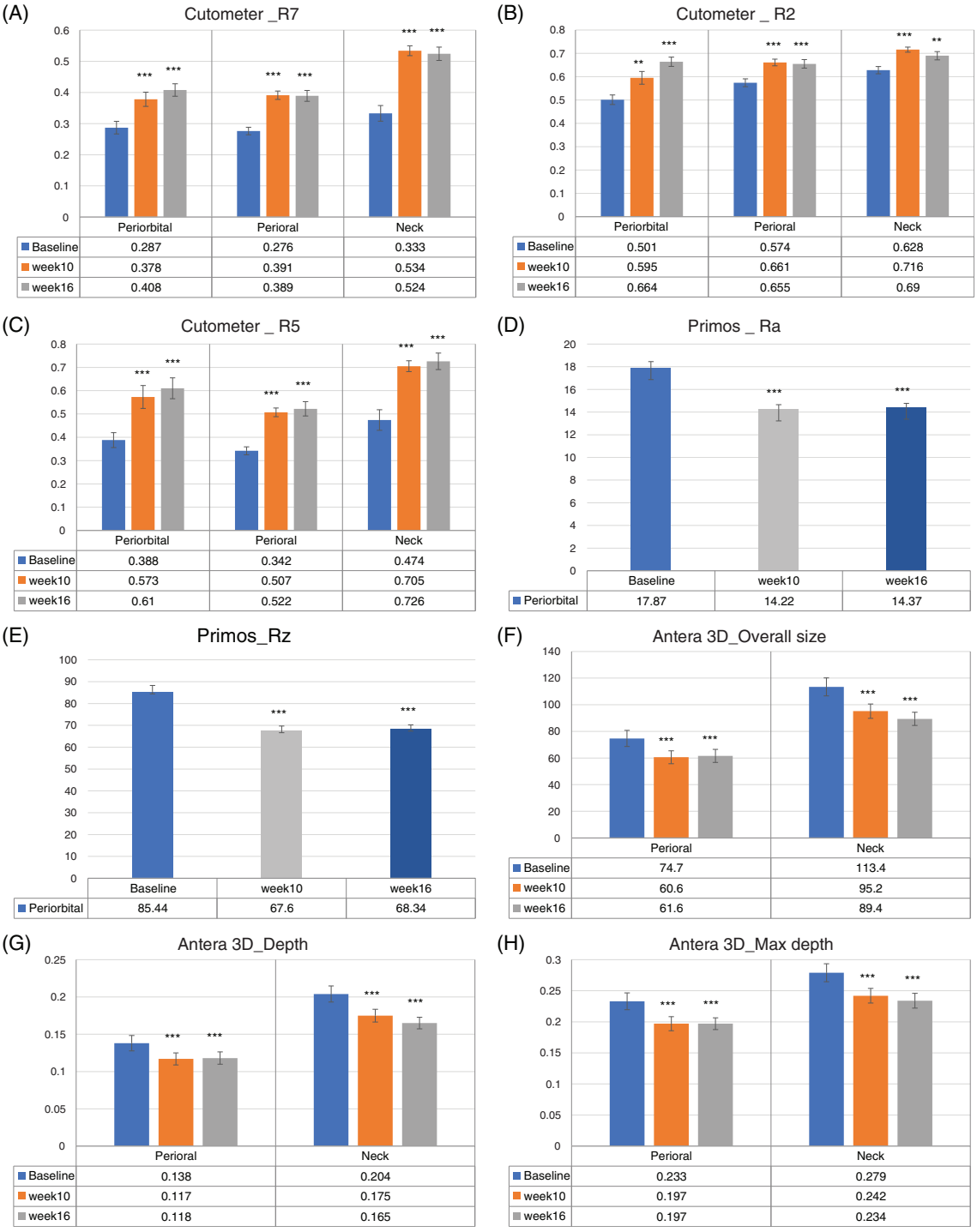
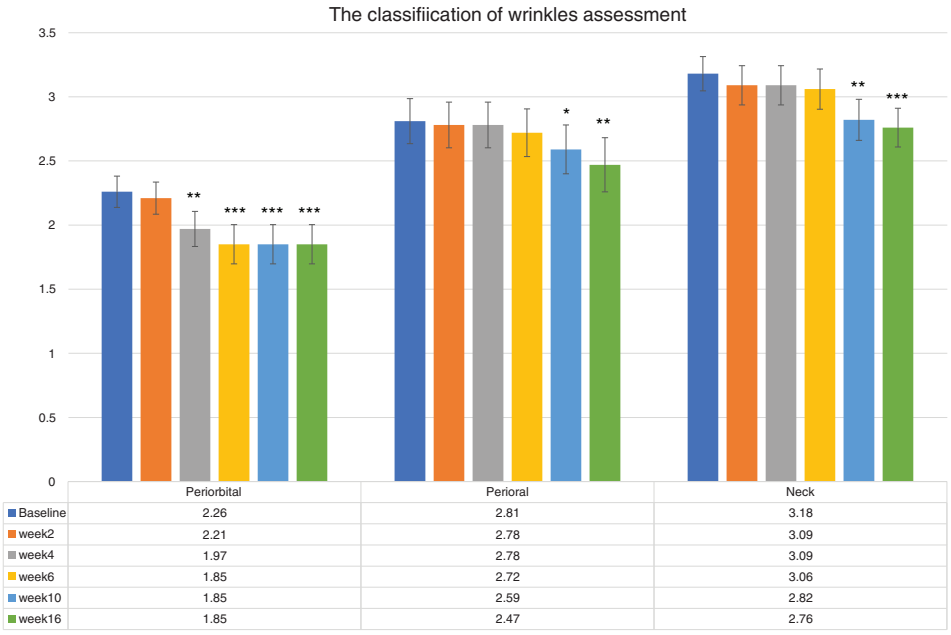


FIGURE 2 Primary and secondary outcomes. ***p <0.001. (A) Changes in Cutometer R7 values measured at 10 and 16 weeks versus baseline. (B) Changes in Cutometer R2 values measured at 10 and 16 weeks versus baseline. (C) Changes in Cutometer R5 values measured at 10 and 16 weeks versus baseline. (D, E) 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).

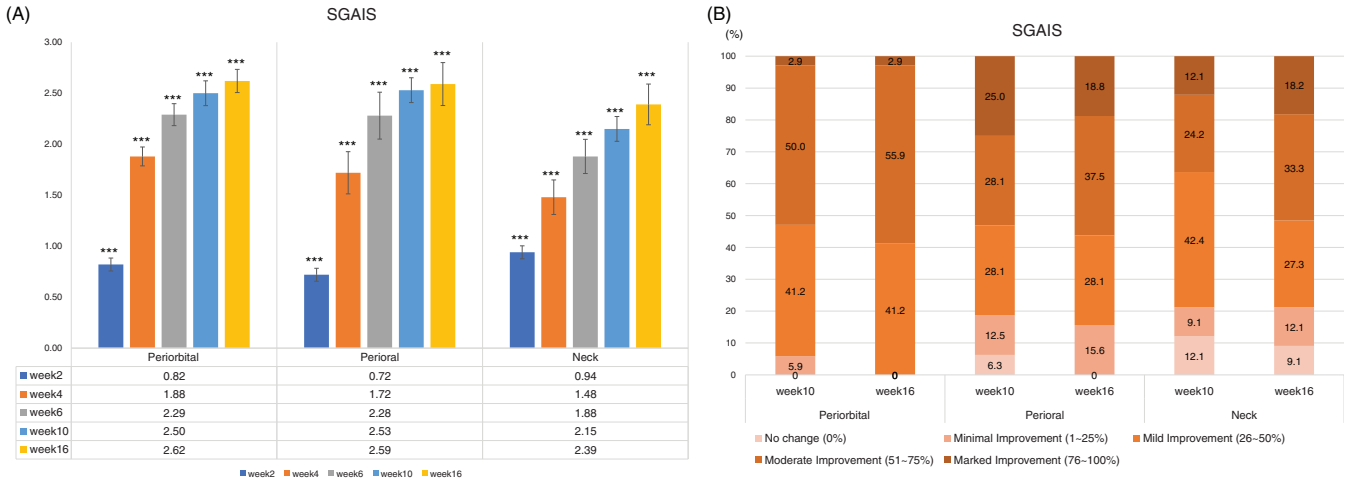
3.4 | Pain NRS evaluation

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,



	Periorbital	Perioral	Neck
Baseline	2.26	2.81	3.18
week2	2.21	2.78	3.09
week4	1.97	2.78	3.09
week6	1.85	2.72	3.06
week10	1.85	2.59	2.82
week16	1.85	2.47	2.76

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



	Periorbital	Perioral	Neck
week2	0.82	0.72	0.94
week4	1.88	1.72	1.48
week6	2.29	2.28	1.88
week10	2.50	2.53	2.15
week16	2.62	2.59	2.39

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

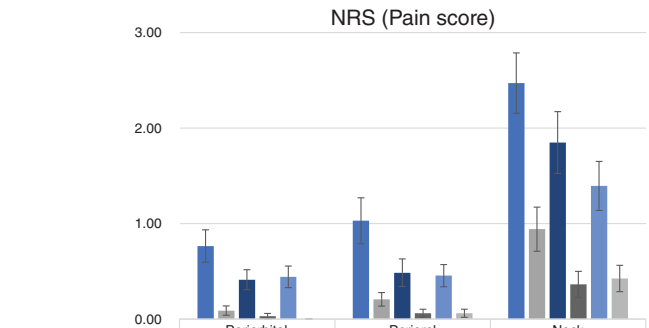
respectively, and decreased as the procedure was repeated (Figure 5). In the neck group, the mean NRS score was greatest at 2.47 ± 1.85, but it decreased over time. One participant complained of residual pain (NRS 1) before the second and third treatments, and at 6, 10, and 16 weeks after the completion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



	Periorbital	Perioral	Neck
immediately after 1st tx	0.76	1.03	2.47
30minute after 1st tx	0.09	0.21	0.94
immediately after 2nd tx	0.41	0.48	1.85
30minute after 2nd tx	0.03	0.06	0.36
immediately after 3rd tx	0.44	0.45	1.39
30minute after 3rd tx	0.00	0.06	0.42

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.

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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.

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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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