Received: 14 April 2023 | Revised: 3 July 2023 | Accepted: 21 July 2023

DOI: 10.1111/jocd.15944

JCD Journal of Cosmetic Dermatology WILEY

ORIGINAL ARTICLE

# The efficacy of intradermal hyaluronic acid filler as a skin quality booster: A prospective, single-center, single-arm pilot study

Joo Hee Lee MD[1] | Jemin Kim MD, PhD[2,3] | Yun Na Lee BS[1] | Sooyeon Choi MD[1] | Young In Lee MD, PhD[1,2] | Jangmi Suk MS[4] | Ju Hee Lee MD, PhD[1,2]

[1]Department of Dermatology and Cutaneous Biology Research Institute, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

[2]Scar Laser and Plastic Surgery Center, Yonsei Cancer Hospital, Yonsei University College of Medicine, Seoul, Korea

[3]Department of Dermatology, Yongin Severance Hospital, Yonsei University College of Medicine, Gyeonggi-do, Korea

[4]Global Medical Research Center, Seoul, Korea

**Correspondence**
Ju Hee Lee, Department of Dermatology and Cutaneous Biology Research Institute, Yonsei University College of Medicine, 50-1 Yonsei Ro, Seodaemun-gu, Seoul 03722, Korea.
Email: juhee@yuhs.ac

## Abstract

**Background:** The use of "skin boosters" comprised of hyaluronic acid (HA)-based fillers to improve skin quality has gained popularity recently, especially in individuals interested in skin rejuvenation.

**Aim:** This study aimed to evaluate the efficacy and safety of intradermal micropuncture injections of HA-based gel filler combined with lidocaine (BYRYZN® SKINBOOSTER HA, ACROSS Co., Ltd., Gangwon-do, Korea).

**Patients/Methods:** A prospective, single-arm, open-label pilot study was conducted with study subjects who were aged between 30 and 60 years old and exhibited evidence of skin aging, such as wrinkles and loss of elasticity. They received three injections at 2-week intervals and were followed up for a total of 12 weeks.

**Results:** Twenty subjects with a mean age of 54.1 years were included. The mean Lemperle wrinkle scale demonstrated a 40% decrease from 2.60 ± 0.60 at baseline to 1.55 ± 0.51 at week 8. The improvement rate was maintained at about 33% until week 12. The average maximum height of the wrinkle (Rz, μm), average skin roughness (Ra, μm), skin elasticity (R2, AU), facial curved length (mm), skin pore size ($mm^2$), skin hydration (AU), TEWL ($g/hm^2$), and skin glossiness (gloss value, AU) exhibited statistically significant improvements over time compared with the baseline measurements. No serious adverse effects or persistent adverse effects were reported, except for a transient subcutaneous nodule in one subject.

**Conclusions:** This study demonstrates that multiple microinjections of HA-based gel filler for facial skin aging are safe and effective in improving facial skin quality.

KEYWORDS
filler, hyaluronic acid, skin aging

Joo Hee Lee and Jemin Kim contributed equally to this work.

## 1 | INTRODUCTION

The appearance of wrinkles is one of the typical signs of the aging process. Skin aging is caused by the loss of hyaluronic acid (HA), subcutaneous adipose tissue, collagen, and elastic fibers over time. HA is a nonsulfated glycosaminoglycan composed of repeating polymeric disaccharides of D-glucuronic acid and N-acetyl-D-glucosamine. It is located near collagen interfaces and elastin fibers, which facilitates the maintenance of their proper configuration.[1] The structure of HA has the remarkable ability to hold approximately 1000 times its weight in water, which contributes to the maintenance of the flexibility and volume of the skin.[1] HA is a nontoxic and nonsensitizing agent as it is produced and separated through streptococcal fermentation with high purity and does not contain biochemically active substances.

Many researchers have investigated the cosmetic efficacies of HA-based formulations, such as gels, creams, and dermal fillers. Subcutaneous injections of HA fillers have been widely used for wrinkle improvement.[2] According to the American Society for Aesthetic Plastic Surgery (ASAPS), HA fillers were reported to have been used in more than 85% of dermal filling cases. Recently developed measures to improve skin aging involve not only improving the depressed volume but also the use of "skin quality boosters," which are comprised of HA-based fillers that increase the elasticity and moisture content of the skin. These are administered through intradermal micropuncture injections.[3,4]

In this study, we analyzed the efficacy and safety of intradermal HA fillers in improving facial skin quality assessed through the wrinkle scale and noninvasive objective biophysical parameters.

## 2 | MATERIALS AND METHODS

### 2.1 | Patient selection

This was a prospective, single-center, single-arm, open-label pilot study. Twenty subjects aged between 30 and 60 years, with signs of skin aging, who met the inclusion and exclusion criteria, were included in the study. The inclusion criteria were: male and female volunteers aged between 30 and 60 years, with decreased skin elasticity and wrinkles on their cheeks with more than 2 points on the Lemperle wrinkle scale.[5] Subjects who met the following criteria were excluded: (a) dermal fillers or botulinum toxin injections within the previous 12 months; (b) other facial wrinkle correction treatments within 6 months; (c) a history or presence of inflammatory/infectious disease, skin graft, keloid or hypertrophic scar on the face; (d) a history or presence of autoimmune disease; (e) having experienced anaphylaxis from any cause or a severe combined allergy; (f) prescribed anti-coagulant therapy within 2 weeks of the screening date; (g) a history of severe cardiopulmonary disease; (h) lactating or pregnant.

This study complied with the principles of the Declaration of Helsinki, Korean Good Clinical Practice, and local regulatory requirements. The study protocols and informed consent form were approved by the Institutional Review Board of our institution (IRB No. 1-2022-0020). All participants provided written informed consent.

### 2.2 | Study design

At the baseline visit (week 0, Visit 1) before the injection, the biophysical parameters of aging were measured using corresponding devices (Table 1), and face photographs were obtained by VISIA-CR (Canfield Scientific). All subjects received baseline injections at Visit 1 (Week 0) and subsequently received two further injections 2 weeks apart (Visit 2 = Week 2, Visit 3 = Week 4). The follow-up assessments were performed two (Visit 4, Week 6), four (Visit 5, Week 8), and eight (Visit 6, Week 12) weeks after the last injection.

### 2.3 | Materials

The BYRYZN® SKINBOOSTER HA (ACROSS Co., Ltd.) is a transparent viscoelastic gel containing monophasic HA at a 20 mg/mL concentration. HA is cross-linked by 1,4-butanediol diglycidyl ether (BDDE), combined with lidocaine HCl (3 mg/mL) and buffered with phosphate-buffered saline at pH 7. It was administered via sterile, 1.1-mL prefilled syringes with 30-gauge, 13 mm needles.

### 2.4 | Injection protocols

Local anesthetic cream (EMLA, lidocaine HCL 2.5% and prilocaine 2.5%) was applied to the area to be treated for 45 min prior to the injection. The treatment area was wiped with povidone-iodine and normal saline. The treatment area was limited to 1 cm below the lower orbital rim to the lower cheek margin. The study material was injected through multiple microinjections, in which relatively small volumes of 0.05 mL were administered per point with a 30-gauge needle at mid-dermis level. After injecting about 20 points on each side 1–2 cm apart (total of 40 points on both cheeks), the injected area was softly massaged for 1–2 min. Following that, ice compress was applied for several minutes to minimize potential side effects such as the hematoma, ecchymosis, and edema formation at the injection site.

### 2.5 | Efficacy evaluation

The primary endpoint used to evaluate the efficacy of the intervention was the improvement in wrinkle scale at weeks 6, 8, and 12. An independent, blinded board-certified dermatologist evaluated the severity of skin wrinkles in the cheek area using the Lemperle wrinkle

**TABLE 1** The objective parameters of skin aging measured in the study.

| Parameters | Measurement devices | Unit of measurement and interpretation |
|---|---|---|
| Skin roughness | PRIMOS® (Phase-shift Rapid In-vivo Measurement Of skin; GFMesstechnik GmbH) | Ra = arithmetic average skin roughness |
| Fine wrinkles | PRIMOS® (Phase-shift Rapid In-vivo Measurement Of skin; GFMesstechnik GmbH) | Rz = average maximum height of the wrinkle |
| Skin elasticity | Cutometer® dual MPA 580 (Courage & Khazaka) | R2 (gross elasticity, Ua/Uf)<br>As skin elasticity improves, the gross elasticity (R2) increases |
| Facial lifting | Morpheus 3D® scanner (Morpheus Co.) | Facial curved length (mm) = the length of the curve from ala of nose to tragus |
| Skin pores | Antera 3D® camera system (Miravex) | Skin pore size ($mm^2$) = The pore area in the unit area measured in skin pore analysis mode |
| Skin hydration | Corneometer® CM 825 (Cour-age & Khazaka)<br>Moisture map® (Courage & Khazaka) – for visualization | As skin hydration increases, the measurement increases |
| TEWL | TEWL® dual MPA 580 (Courage & Khazaka) | As the skin barrier function improves, the TEWL decreases |
| Skin glossiness | Glossymeter® (Courage & Khazaka) | As skin glossiness increases, the measurement increases |

*Note*: The unit of measurements and its interpretations were derived from previous studies.[6–10]
Abbreviations: AU, artificial unit; R2, visco-elasticity in %; TEWL, transepidermal water loss.

scale devised in 2001 and revised in 2015.[5] The face photographs obtained during every visit were used for this evaluation. Secondary efficacy measures included average maximum height of the wrinkle (Rz, μm), average skin roughness (Ra, μm), skin elasticity (R2, AU), facial curved length (mm), skin pore size ($mm^2$), skin hydration (AU), transepidermal water loss (TEWL, $g/hm^2$), and skin glossiness (gloss value, AU) at weeks 6, 8, and 12. The degree of overall improvement was also assessed at Visits 4, 5, and 6 by the investigators and the subjects using the Global Aesthetic Improvement Scale (GAIS): 1 = worse, 2 = no change, 3 = improved, 4 = much improved, 5 = very much improved.

### 2.6 | Safety measures

At each visit, vital signs were measured and physical examinations were undertaken for each patient. The investigators examined the injection sites for adverse effects at each follow-up visit. In addition, after every treatment session, the subjects were monitored for at least 30 min for possible adverse events, such as hemorrhage, pain, induration, swelling, redness, pruritus, or granuloma formation. The subjects were also asked to evaluate their degree of pain using visual analog scale (100 mm scale) 30 min after the injection.

### 2.7 | Statistical analyses

Data are presented as numbers (percentages) or means ± standard deviations. Repeated measures analysis of variance (RM-ANOVA) and subsequent post hoc analysis with the paired *t*-test with the Bonferroni correction was performed to compare and incorporate parameters at each time point. Statistical analyses were conducted using the SPSS version 25.0 (IBM Corp.). Differences of $p < 0.05$ were considered statistically significant.

## 3 | RESULTS

### 3.1 | Subjects

A total of 20 female subjects were recruited for the study from July to December 2022. Although the initial inclusion criteria allowed for subjects aged between 30 and 60 years, the actual age of enrolled subjects ranged between 39 and 59 years (mean 54.1 years). All subjects completed the study process along with the 12-week follow-up period. During the baseline Lemperle wrinkle scale assessment before the injection, nine of the participants (45%) were assessed as grade 2, 10 (50%) as grade 3, and one (5%) as grade 4.

### 3.2 | Efficacy evaluation

The measurements of objective parameters of skin aging evaluated in this study at the baseline and follow-up time points are summarized in Table 2. A 40.4% decrease was observed in the mean Lemperle wrinkle scale, from 2.60 ± 0.60 at baseline to 1.55 ± 0.51 at week 8. The improvement rate was maintained at about 33% until week 12. Eighteen (90%) and 12 (75%) subjects exhibited a greater than or equal to the 1-point improvement on the Lemperle wrinkle scale at week 8 and week 12, respectively. RM-ANOVA and subsequent post hoc analysis revealed an overall significant improvement in the wrinkle scale during the study period as well as significant differences in the wrinkle scale between all follow-up appointments and baseline.

Measurements of the average maximum height of the wrinkle (Rz, μm), average skin roughness (Ra, μm), skin elasticity (R2 index), facial curved length (mm), and skin pore size ($mm^2$) demonstrated statistically significant improvements over time compared with the baseline measurements. The average skin roughness (Ra) and height of the wrinkles (Rz) demonstrated a significant decrease over time

**TABLE 2** Evaluation of the objective parameters of skin aging.

| Parameters | Baseline | Week 6 | Week 8 | Week 12 | *p*-Value[†] |
|---|---|---|---|---|---|
| Lemperle wrinkle scale | 2.60 ± 0.60 | 1.85 ± 0.59 | 1.55 ± 0.51 | 1.75 ± 0.72 | <0.001 |
| Improvement rate (%)[a] | | 28.8 | 40.4 | 32.7 | |
| *p*-Value[‡] | | <0.001 | <0.001 | <0.001 | |
| Average maximum height of the wrinkle (Rz, μm) | 84.21 ± 12.73 | 79.98 ± 11.13 | 76.16 ± 11.93 | 73.73 ± 11.68 | <0.001 |
| Improvement rate (%)[a] | | 5.0 | 9.6 | 12.4 | |
| *p*-Value[‡] | | <0.001 | <0.001 | <0.001 | |
| Average skin roughness (Ra, μm) | 17.11 ± 2.85 | 16.22 ± 2.72 | 15.53 ± 2.61 | 14.98 ± 2.74 | <0.001 |
| Improvement rate (%)[a] | | 5.2 | 9.3 | 12.4 | |
| *p*-Value[‡] | | <0.001 | <0.001 | <0.001 | |
| Skin elasticity (R2, AU) | 0.66 ± 0.05 | 0.68 ± 0.05 | 0.70 ± 0.05 | 0.73 ± 0.04 | <0.001 |
| Improvement rate (%)[b] | | 2.9 | 5.9 | 9.4 | |
| *p*-Value[‡] | | <0.001 | <0.001 | <0.001 | |
| Facial curved length (mm) | 115.24 ± 3.38 | 117.04 ± 3.59 | 118.20 ± 3.44 | 119.57 ± 3.58 | <0.001 |
| Improvement rate (%)[b] | | 1.6 | 2.6 | 3.8 | |
| *p*-Value[‡] | | <0.001 | <0.001 | <0.001 | |
| Skin pore size ($mm^2$) | 28.34 ± 15.57 | 24.95 ± 13.50 | 22.00 ± 11.62 | 20.84 ± 11.44 | <0.001 |
| Improvement rate (%)[a] | | 12.0 | 22.4 | 26.5 | |
| *p*-Value[‡] | | <0.001 | <0.001 | <0.001 | |
| Skin hydration (AU) | 43.06 ± 9.25 | 52.72 ± 8.59 | 60.43 ± 8.13 | 63.03 ± 7.88 | <0.001 |
| Improvement rate (%)[b] | | 22.4 | 40.3 | 46.4 | |
| *p*-Value[‡] | | <0.001 | <0.001 | <0.001 | |
| TEWL ($g/hm^2$) | 12.90 ± 2.10 | 11.85 ± 2.09 | 11.05 ± 2.07 | 10.81 ± 2.25 | <0.001 |
| Improvement rate (%)[a] | | 8.1 | 14.3 | 16.2 | |
| *p*-Value[‡] | | <0.001 | <0.001 | <0.001 | |
| Skin glossiness (gloss value, AU) | 10.88 ± 2.53 | 11.87 ± 2.51 | 12.55 ± 2.76 | 12.74 ± 2.84 | <0.001 |
| Improvement rate (%)[b] | | 9.1 | 15.4 | 17.1 | |
| *p*-Value[‡] | | <0.001 | <0.001 | <0.001 | |

*Note*: Data are represented by (mean ± SD, [% change]).

Abbreviations: AU, artificial unit; R2, visco-elasticity in %; TEWL, transepidermal water loss.

[a]Defined as (Initial week measurement − follow-up measurement)/initial measurement × 100%.

[b]Defined as (follow-up week measurement − initial measurement)/initial measurement × 100%.

[†]RM two-way ANOVA, with the Greenhouse–Geisser correction.

[‡]Post hoc analysis of each time point by paired *t*-test with Bonferroni's correction, where $p < 0.0125$ was considered significant.

at weeks 6, 8, and 12 ($p < 0.001$). The improvement rate relative to the baseline value was 12.4% at week 12. The skin elasticity significantly increased over time, from 0.66 ± 0.05 AU (artificial unit) at baseline to 0.70 ± 0.05 AU and 0.73 ± 0.04 AU at weeks 8 and 12, respectively. There was also a significant improvement in both the facial curved length measured by Morpheus 3D® scanner and the skin pore size assessed through Antera 3D® camera system.

Skin hydration, which was measured by Corneometer®, significantly increased from 43.06 ± 9.25 AU at baseline to 63.03 ± 7.88 AU at week 12 ($p < 0.001$). Conversely, TEWL demonstrated a significant decrease over the study period (from 12.90 ± 2.10 $g/hm^2$ at baseline to 10.81 ± 2.25 $g/hm^2$ at week 12 ($p < 0.001$)). Moreover, the skin glossiness increased from 10.88 ± 2.53 AU at baseline to 12.55 ± 2.76 AU and 12.74 ± 2.84 AU at weeks 8 and 12, respectively. Figures 1 and 2 demonstrate the individual representative results of visualizable parameters (wrinkle, roughness, pore, hydration – moisture map).

GAIS assessment recorded by the subjects and investigators was regarded as an "improvement" if it was scored 3-points (improved) or above (4-much improved, 5-very much improved). The proportion of scores classified as "improvement" was 87.5% at week 6, 85% at week 8, and 85% at week 12 (Figure 3). One subject was assessed as "worse" due to a transient side effect at week 8. However, the assessment changed to "much improved" at week 12.

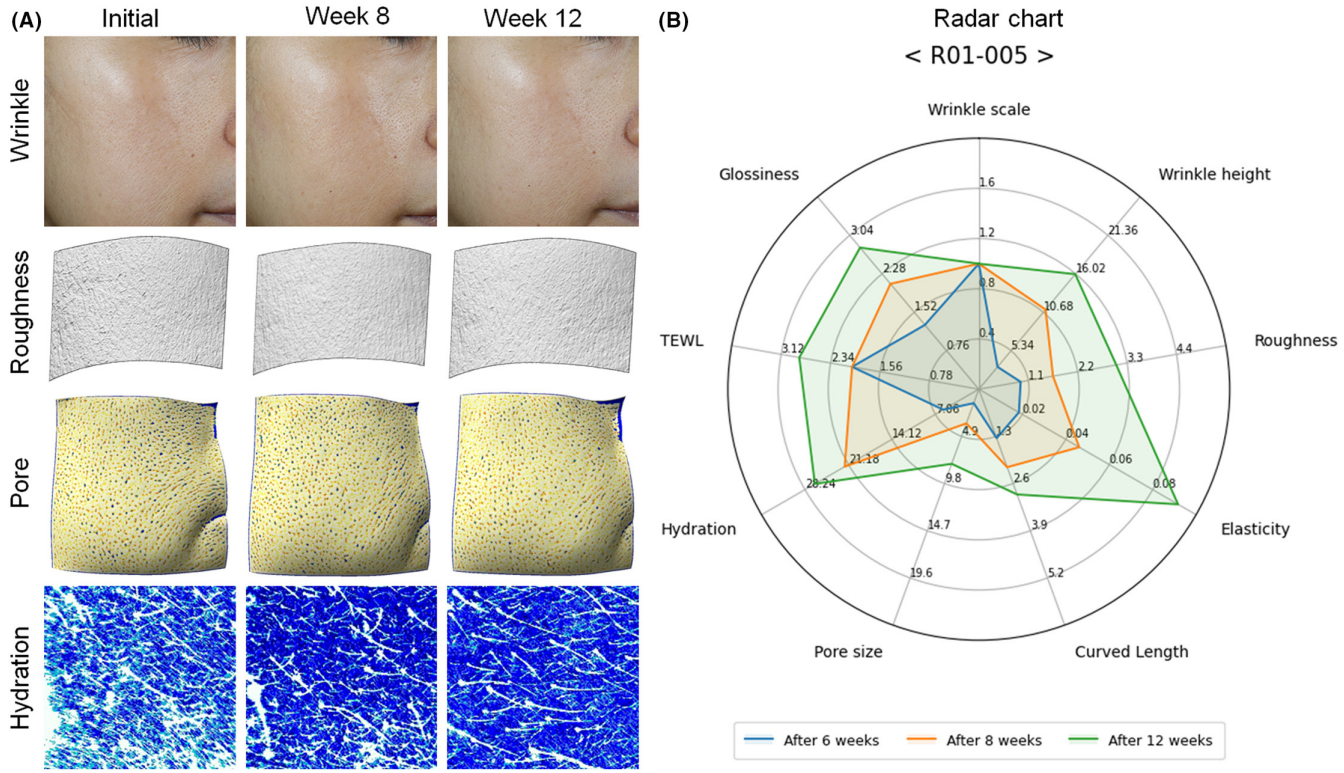


FIGURE 1 (A) Representative images of subject number 5, depicting skin wrinkles, skin roughness (visualized by PRIMOS®), skin pores (visualized by Antera 3D®), and skin hydration (visualized by Moisture map®) at baseline, week 8, and week 12. (B) A radar chart represents the absolute value changes in the objective biophysical parameters of subject number 5. In order to determine the scale for each indicator, the maximum value of all subjects for each parameter was divided into five equal parts.

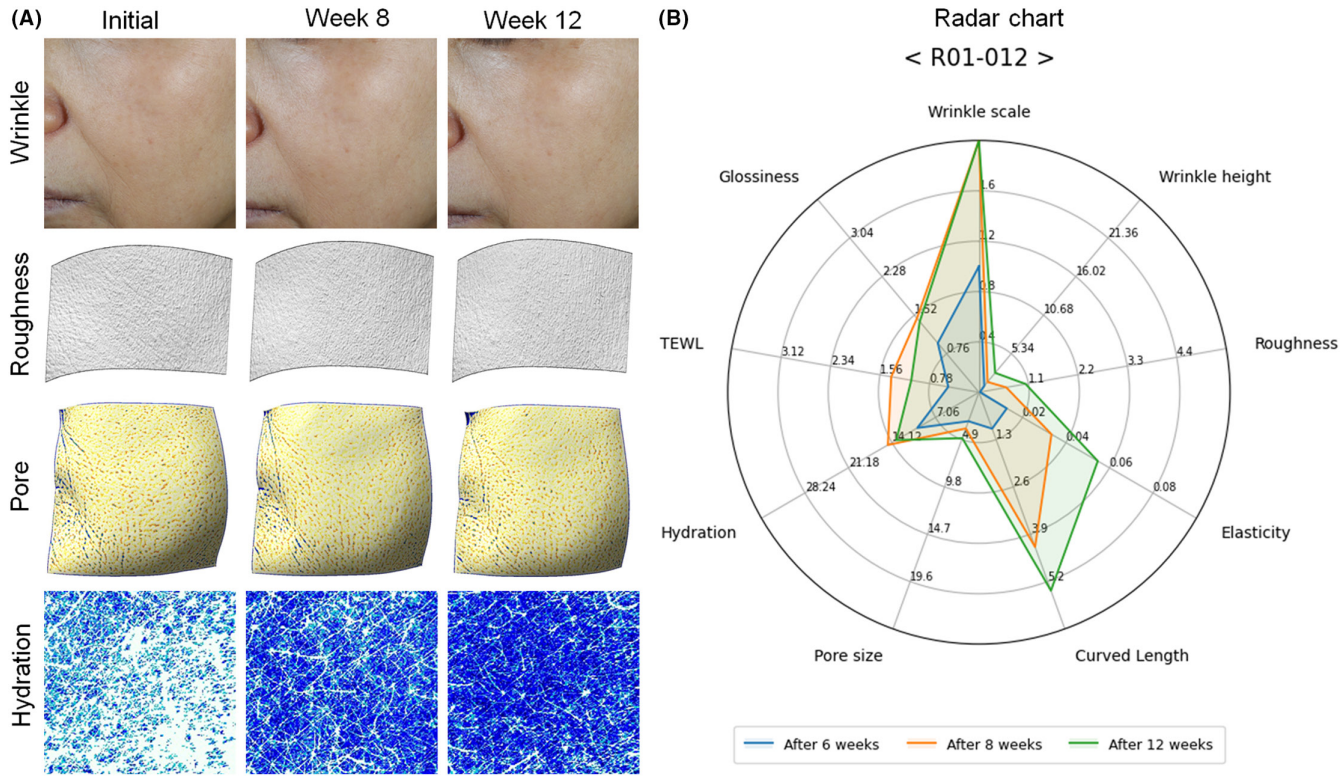


FIGURE 2 (A) The representative images of subject number 12, depicting skin wrinkles, skin roughness (visualized by PRIMOS®), skin pores (visualized by Antera 3D®), and skin hydration (visualized by Moisture map®) at baseline, week 8, and week 12. (B) A radar chart represents the absolute value changes in the objective biophysical parameters of subject number 12. In order to determine the scale for each indicator, the maximum value of all subjects for each parameter was divided into five equal parts.

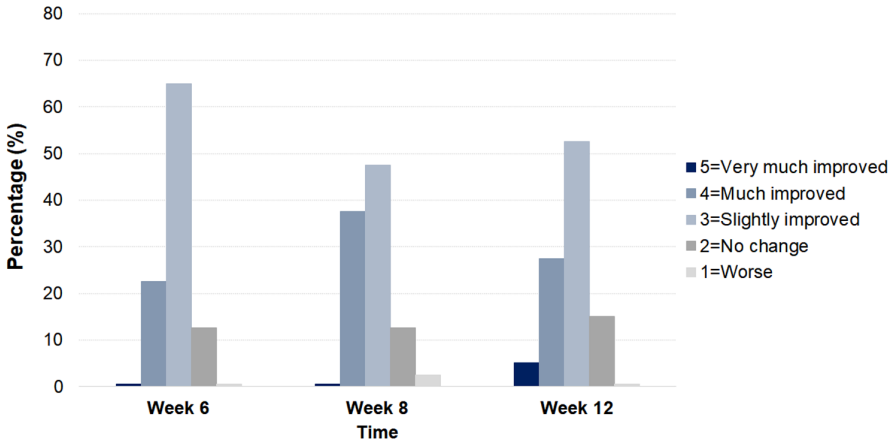


**FIGURE 3** The results of the Global Aesthetic Improvement Scale (GAIS), which was assessed by study subjects and investigators.

### 3.3 | Safety evaluation

The study product was well-tolerated, and the adverse reactions were mostly mild and transient. The most commonly reported transient adverse effect was the formation of an injection site bruise. However, most of these improved 1–2 weeks after the injection. One subject experienced the development of a subcutaneous nodule with a bruise at the injection site at week 6, which improved without any intervention after 2 weeks. The mean score of pain level assessed using VAS (100 mm scale) was 37.05 ± 22.08 for the first injection. The pain scores decreased over time to 28.65 ± 16.42 for the second injection and 30.55 ± 17.51 for the third injection.

## 4 | DISCUSSION

The present study investigated the efficacy and safety of HA fillers in improving facial skin aging. The participants were treated with three injection sessions two weeks apart and followed up for a total of 12 weeks. The study material, BYRYZN® SKINBOOSTER HA, also referred to as "skin quality boosters (SQB)" was injected through multiple microinjections. Significant improvements in wrinkle scale and biophysical parameters were observed. No serious adverse effects or persistent adverse effects were reported, except for a transient subcutaneous nodule experienced by one subject.

Hyaluronic acid is well known for its role in skin rejuvenation due to its viscoelastic properties.[11] A placebo-controlled study demonstrated that injections of nonanimal stabilized hyaluronic acid could stimulate collagen production through mechanical compression and stretching, as well as activation of collagen-producing fibroblast and induction of profibrotic growth factors.[12,13] In addition, intradermal injections of HA as SQB fillers encourage an improvement in the skin's overall condition by drawing water into the extracellular matrix. This process helps restore the skin's hydration balance, enhance skin elasticity, and refine dermal microstructure.[14,15] Recent studies have reported that HA is also involved in the angiogenesis,[16] and immune regulation processes,[17,18] which can contribute to skin rejuvenation.[19]

Figure 4 illustrates the mean changes in absolute value or improvement rate in biophysical parameters of aging for all subjects, over the study period duration. The wrinkle scale demonstrated lesser improvement than did the other parameters, with a slight decrease in the improvement rate from week 8 to 12. However, skin hydration, TEWL, elasticity, and glossiness continued to improve throughout the study period. The SQB filler used in the study was composed of smaller HA particles with low cross-linking, high cohesivity, and low complex viscosity, which enables it to distribute uniformly and integrate with the surrounding tissue.[20,21] Although SQB filler has a less viscous gel structure and produces a weaker lifting effect than do conventional fillers, it is easily absorbed and interacts well with the native HA in the skin's extracellular matrix.[22] Thus, it appears more natural in the superficial dermis and contributes to skin hydration and elasticity with a long-lasting effect.[23]

Limitations of our study include its relatively small sample size, lack of a control group, and absence of male subjects. Moreover, due to this study's relatively short follow-up period, the assessment of the long-term efficacy and safety of the SQB filler was limited. However, several studies have indicated the long-lasting effects of booster injections in terms of skin elasticity.[11,15] In addition, prior studies have reported a seasonal variation in skin hydration and elasticity in Korea. Specifically, these metrics tend to decrease during the cold and dry winter and increase in the spring, which can serve as a confounding factor. However, in the present study, which was conducted from summer through winter, a significance improvement in skin barrier function and elasticity was observed, despite the potential disadvantage posed by seasonal factors.[24] This study utilized several noninvasive skin biophysical parameters to gauge the retention of SQB fillers. This could supplement the evaluation of effectiveness and aid in determining the durability of the SQB filler.

In conclusion, the present study demonstrated that transdermal injections of HA-based gel filler are safe and effective in improving the quality of facial skin in terms of wrinkles, elasticity, pores, hydration, and glossiness. Future randomized clinical trials with larger sample sizes and longer study periods are required to confirm its long-term efficacy, durability, and safety.

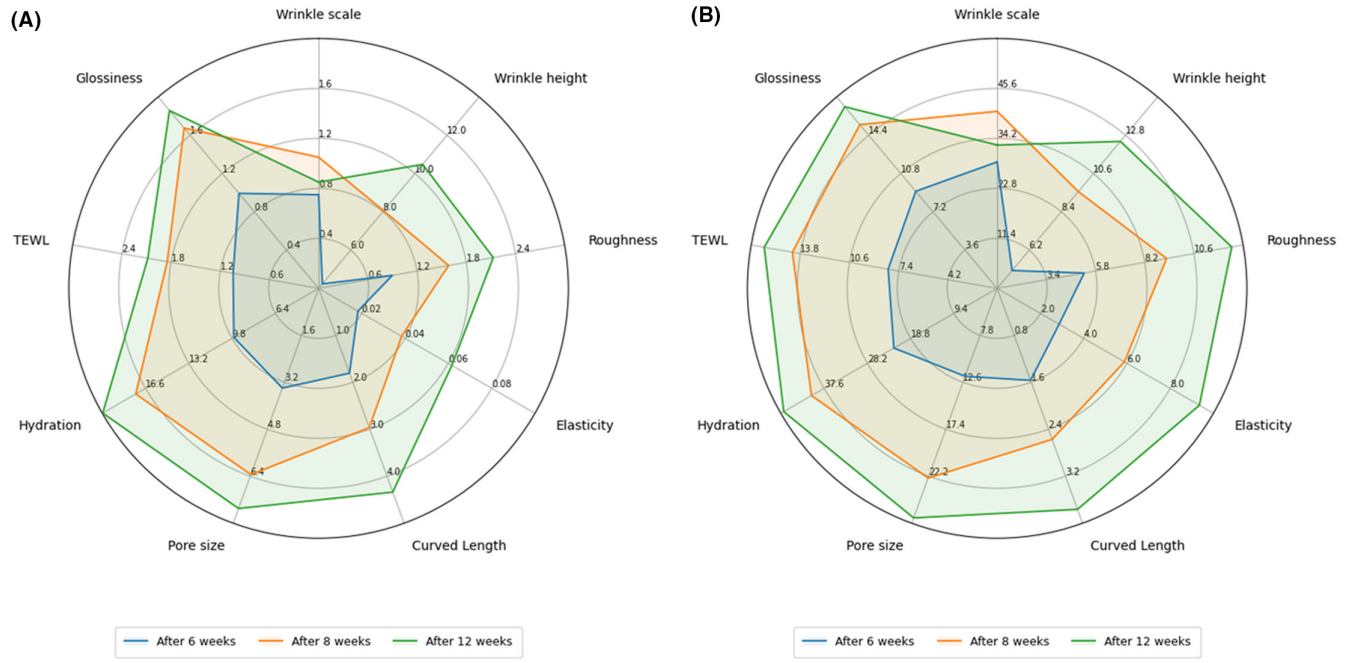


FIGURE 4 (A) A radar chart represents the mean absolute value changes in objective biophysical parameters for all subjects. (B) This chart depicts the mean changes in the improvement rate (percentage) of objective biophysical parameters for all subjects. The scale of each index was divided into five equal parts after setting −1.5 standard deviation (SD) as the minimum value and +1.5 SD as the maximum value of each parameter.

## AUTHOR CONTRIBUTIONS

Dr Kim and Dr Lee had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Ju Hee Lee. Acquisition, analysis, or interpretation of data: Joo Hee Lee, Sooyeon Choi, Jemin Kim, Jangmi Suk. Drafting of the manuscript: Joo Hee Lee, Jemin Kim. Critical revision of the manuscript for important intellectual content: Young In Lee, Ju Hee Lee. Statistical analysis: Jemin Kim, Yun Na Lee. Administrative, technical, or material support: Jemin Kim, Yun Na Lee, Sooyeon Choi. Supervision: Ju Hee Lee, Young In Lee.

## ACKNOWLEDGMENTS

The study material (BYRYZN® SKINBOOSTER HA, ACROSS Co., Ltd., Gangwon-do, Korea) was provided by ACROSS Co., Ltd. However, ACROSS Co., Ltd. had no role in the study design, implementation, data collection, data analysis, data interpretation, manuscript preparation, manuscript review, or manuscript approval.

## CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest regarding the paper.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## ETHICS STATEMENT

This study complied with the principles of the Declaration of Helsinki, Korean Good Clinical Practice, and local regulatory requirements. The study protocols and informed consent form were approved by the Institutional Review Board of Severance Hospital (IRB No. 1-2022-0020). All participants provided written informed consent.

## ORCID

*Joo Hee Lee* https://orcid.org/0000-0002-7379-1195
*Jemin Kim* https://orcid.org/0000-0001-6628-3507
*Young In Lee* https://orcid.org/0000-0001-6831-7379

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**How to cite this article:** Lee JH, Kim J, Lee YN, et al. The efficacy of intradermal hyaluronic acid filler as a skin quality booster: A prospective, single-center, single-arm pilot study. *J Cosmet Dermatol*. 2024;23:409-416. doi:10.1111/jocd.15944