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To cite this article: So Young Lee, Choon Shik Youn & Kui Young Park (2026) Midface volumization and skin quality enhancement with a hyaluronic acid–polynucleotide hybrid filler: a 24-week prospective open-label study, Journal of Dermatological Treatment, 37:1, 2621537, DOI: [10.1080/09546634.2026.2621537](https://doi.org/10.1080/09546634.2026.2621537)

To link to this article: <https://doi.org/10.1080/09546634.2026.2621537>



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Published online: 02 Feb 2026.



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RESEARCH ARTICLE



Midface volumization and skin quality enhancement with a hyaluronic acid–polynucleotide hybrid filler: a 24-week prospective open-label study

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ABSTRACT

Background: Facial aging is characterized by midface volume loss from structural and dermal atrophy. **Objectives:** To evaluate the efficacy and safety of a hyaluronic acid–polynucleotide (HA–PN) hybrid filler for temporary restoration of anteromedial cheek volume.

Methods: In this single-center, open-label trial, 15 adults with moderate-to-severe anteromedial cheek volume loss (Mid-Face Volume Deficit Scale [MFVDS] score ≥ 3) received up to 1 mL HA–PN hybrid filler per side. Evaluations at baseline and weeks 4, 12, and 24 comprised blinded photographic MFVDS rating (primary endpoint: ≥ 1 -grade improvement at week 4), GAIS (Global Aesthetic Improvement Scale) score, participant satisfaction, transepidermal water loss, skin hydration, elasticity, and adverse events.

Results: All participants completed the study without serious adverse events. MFVDS scores improved significantly at week 4 and remained improved through weeks 12 and 24. GAIS and satisfaction scores paralleled these gains. Transepidermal water loss decreased and hydration increased over time, and Cutometer parameters (R2 R5 R7) showed progressive improvements in elasticity, indicating enhanced skin quality along with midface volumization.

Conclusions: The HA–PN hybrid filler demonstrated improvements in midface volume restoration with concurrent improvements in skin barrier function, hydration, and elasticity, and was well tolerated over 24 weeks within the constraints of the study design.

ARTICLE HISTORY

Received 1 December 2025

Accepted 20 January 2026

KEYWORDS

Hyaluronic acid; polynucleotide; hybrid filler; midface volume; aesthetic dermatology

Introduction

Facial aging results from soft-tissue atrophy, fat-compartment remodeling, ligament laxity, and skeletal resorption. The midface, particularly the anteromedial cheek, is central to maintaining youthful contours and facial symmetry (1,2). Consequently, nonsurgical volumization with dermal fillers has become a preferred approach because it offers predictable outcomes and minimal downtime (3).

Hyaluronic acid (HA) fillers remain the mainstay of midface augmentation because of their biocompatibility and reversibility; however, biodegradation limits their durability. Most clinical series report effects lasting approximately 8–12 months, with variability across facial subunits and products (4–6).

PNs (Polynucleotides) and polydeoxyribonucleotide (PDRN) are DNA-derived biopolymers that activate A2A adenosine receptor signaling and/or serve as nucleoside sources in the salvage pathway (7–9). Through these mechanisms, they exert anti-inflammatory effects, stimulate fibroblast proliferation, enhance angiogenesis, and promote collagen and elastin synthesis and wound repair. These cutaneous bioactivities provide a mechanistic rationale for combining PN with HA to achieve both immediate space-occupying support and biologic tissue revitalization.

Emerging clinical evidence supports this strategy. In subjects with moderate-to-severe nasolabial folds, protocols using PN (PN-HPT[®]) with cross-linked HA were superior to HA alone on validated aesthetic endpoints, with acceptable safety (10). For the midface, physician-reported scales such as the Mid-Face Volume Deficit Scale (MFVDS) enable standardized efficacy assessment and have been

validated, including in Asian cohorts; the Global Aesthetic Improvement Scale (GAIS) complements these outcomes (2,3).

We conducted a single-center, open-label clinical trial in Korean adults to evaluate the efficacy and safety of an HA–PN hybrid filler for temporary restoration of anteromedial cheek volume. The primary endpoint was blinded photographic MFVDS score; secondary endpoints included GAIS score and biophysical skin metrics (e.g., transepidermal water loss [TEWL], hydration, and elasticity).

Materials and methods

Study design

This single-center, open-label, nonrandomized, single-arm clinical trial with blinded independent photographic evaluation was conducted in the Department of Dermatology, Chung-Ang University Hospital (Seoul, Republic of Korea). The protocol was approved by the relevant institutional review board (IRB No. 2406-021-604) and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Participants

Inclusion criteria: Eligible participants were healthy adults (30–60 years) seeking midface augmentation with anteromedial cheek MFVDS score ≥ 3 (moderate) who provided written informed consent and agreed to avoid other aesthetic procedures during the study.

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Exclusion criteria: Key exclusion criteria were recent use of anticoagulants or facial fillers (HA, PN, or CaHA [calcium hydroxylapatite] within 12 months), active skin infection or inflammation, allergy to HA, PN, or lidocaine, serious systemic disease, pregnancy, or psychological unsuitability.

Intervention

Each subject received up to 1 ml (0.5 ml per side) of Renefil Ultra Plus No. 3 (20 mg/mL cross-linked HA, 1.875 mg/mL polynucleotide and 3.2 mg/mL; 0.3% lidocaine hydrochloride) (BMI Korea Co., Ltd., Gyeonggi, Korea) administered subdermally to the anteromedial cheeks with a 29-gauge needle using a linear threading technique. The product exhibits a storage modulus (G') of approximately 388 Pa, a loss modulus (G'') of 94 Pa, and a complex viscosity of approximately 3,178 Pa·s, indicating an elastic-dominant viscoelastic profile ($\tan \delta \approx 0.24$). Aspiration was routinely performed before each injection pass. Immediately after injection, the treated areas were gently massaged to ensure even filler distribution and a natural contour. All injections were performed by a single experienced dermatologist using aseptic technique to minimize the risk of complications. Postprocedure care included cold compression and avoidance of pressure or heat for 48 h.

Photography standardization

Clinical photographs were captured using a Canon EOS 800D digital SLR camera equipped with a Canon EF 100 mm f/2.8L Macro IS USM lens to ensure high-resolution detail of skin textures. The camera was set to Manual (M) mode to maintain consistent exposure parameters throughout the study (e.g., ISO 100, f/11, and 1/125 s).

Outcome measures

The primary endpoint was the effectiveness and durability of volume enhancement, assessed by clinical evaluation and serial photography at baseline, immediately postprocedure, and at 2, 4, and 24 weeks. Secondary endpoints were changes in skin hydration, barrier function, and elasticity, measured by TEWL, Corneometer values, and Cutometer-derived elasticity indices at each follow-up visit. TEWL was measured using a Tewameter TM300 (Courage+Khazaka, Germany), skin hydration with a Corneometer CM825 (Courage+Khazaka), and elasticity with a Cutometer Dual MPA580. All measurements were performed on the central anteromedial cheek, 2 cm below the infraorbital rim. Room temperature (22–24 °C) and humidity (40–50%) were controlled and kept constant for all assessments. Cutometer analysis included R2, R5, and R7, which respectively represent overall viscoelastic recovery, intrinsic elastic recoil, and biological elasticity. These measurements were chosen because they are established, reproducible tools for quantifying skin biophysical properties and are widely used in dermatologic research to assess treatment-related changes.

MFVDS assessment

At each visit, midface volume was assessed using the MFVDS by the investigator and an independent blinded evaluator. Both evaluators were blinded to treatment time points and clinical information. Prior to study initiation, evaluators underwent calibration and consensus training using representative images to minimize interrater variability. Formal interrater reliability statistics were not calculated due to the exploratory nature and limited sample size of

this pilot study. The MFVDS has been validated as a reliable scale for assessing midface volume deficiency in clinical studies. Participants were graded on a 5-point scale (1, minimal volume loss; 2, mild volume loss; 3, moderate volume loss; 4, severe volume loss; and 5, extreme volume loss).

GAIS evaluation

GAIS assessments were performed by two independent, blinded dermatologists, who evaluated pre- and post-treatment images. Participants were graded on a 5-point scale (1, worsening; 2, slight worsening; 3, no change; 4, slight improvement; and 5, significant improvement). Evaluations were performed separately for the left and right sides of the face, and the overall GAIS score was calculated as the mean of both sides.

Participant satisfaction assessment

Participants self-reported their overall satisfaction with the treatment outcome on a 5-point scale (1, dissatisfied; 2, slightly dissatisfied; 3, neutral; 4, slightly satisfied; and 5, highly satisfied).

Adverse event monitoring

Adverse events were documented immediately after the procedure and at each follow-up visit on the basis of physician evaluation and patient-reported symptoms. For each event, onset and resolution dates, severity, causality, and required interventions were recorded.

Statistical analysis

Descriptive statistics were calculated for all parameters. Continuous variables are presented as mean $\pm$ standard deviation (SD). Normality of data distribution was assessed using the Shapiro–Wilk test. For normally distributed variables, paired t tests were used, whereas Wilcoxon signed-rank tests were applied for non-normally distributed data. Categorical variables were analyzed using McNemar tests. All tests were two-sided, and a P value $< .05$ was considered statistically significant. Given the exploratory design and small sample size, 95% confidence intervals were not systematically calculated, and statistical findings were interpreted as hypothesis-generating. Analyses were performed on the per-protocol and safety sets.

Results

A total of 15 Korean women (mean age, 45.0 ± 8.7 years) completed the study. No protocol deviations or participant withdrawals occurred. No missing data were recorded for any clinical assessments or instrumental measurements, permitting complete-case analysis for all outcome measures.

MFVDS evaluation

MFVDS scores improved markedly from baseline (3.33 ± 0.49), with significant reductions at week 4 (1.00 ± 0.63 ; $p < .001$), week 12 (1.13 ± 0.64 ; $p < .001$), and week 24 (1.60 ± 0.74 ; $p < .001$) (Figure 1).

Representative clinical outcomes

Representative clinical photographs from a participant with a typical response to treatment are shown in Figure 2. Baseline images

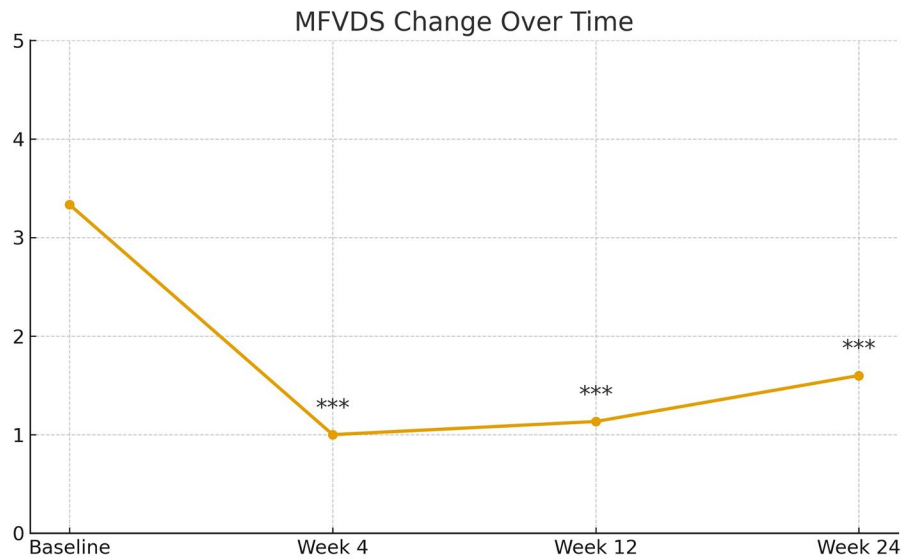


Figure 1. Changes in Mid-Face Volume Deficit Scale (MFVDS) scores over time. MFVDS scores were assessed at baseline and at weeks 4, 12, and 24 after treatment. Error bars indicate standard deviations.

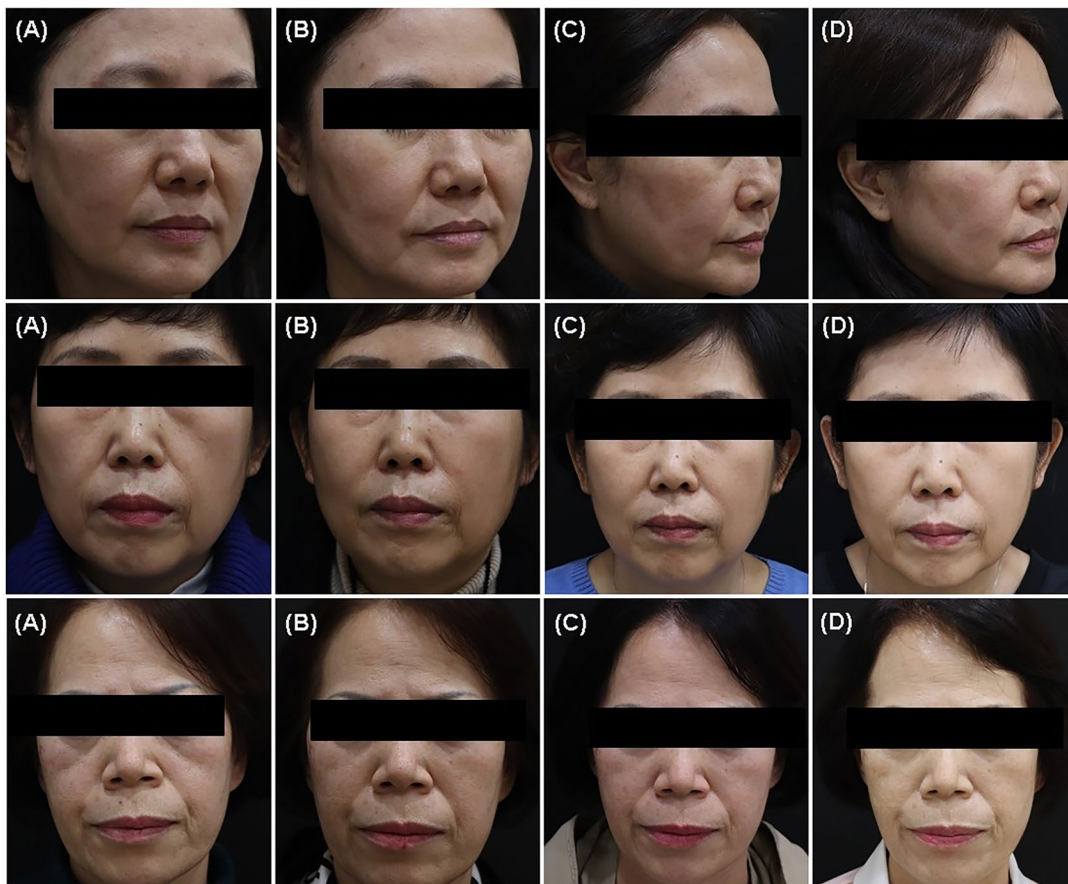


Figure 2. Representative clinical photographs of a participant. Images were obtained at baseline (A) and at weeks 4 (B), 12 (C), and 24 (D) after treatment under standardized conditions.

demonstrated noticeable anteromedial cheek hollowing corresponding to an MFVDS score of 3. At 4, 12, and 24 weeks after injection, restoration of midface contour and improved cheek fullness were observed, consistent with the MFVDS improvements. Skin quality

parameters, including surface smoothness and overall skin vitality, also showed visible enhancement over time, supporting the instrumental findings of increased hydration and elasticity. Written consent for publication of de-identified images was obtained from all participants.

GAIS and participant satisfaction

Investigator-assessed GAIS scores demonstrated consistent aesthetic improvement: all participants were rated as “very much improved” (score 5) at weeks 4 and 12, with a slight decrease to 4.67 ± 0.49 at week 24 (Figure 3). Participant satisfaction paralleled GAIS findings, remaining high at week 4 (5.0) and declining slightly at weeks 12 and 24 (4.93 ± 0.26 and 4.40 ± 0.63 , respectively) (Figure 4).

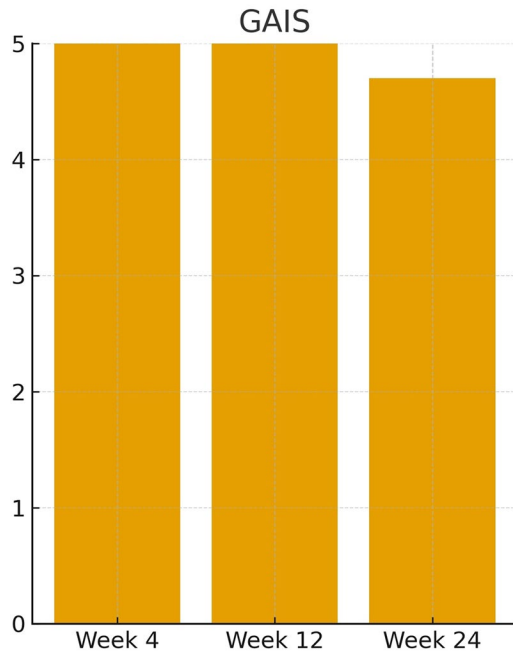


Figure 3. Investigator-assessed Global Aesthetic Improvement Scale (GAIS) scores over time. GAIS evaluations were performed by blinded investigators at each follow-up visit. Data are presented as mean ± SD.

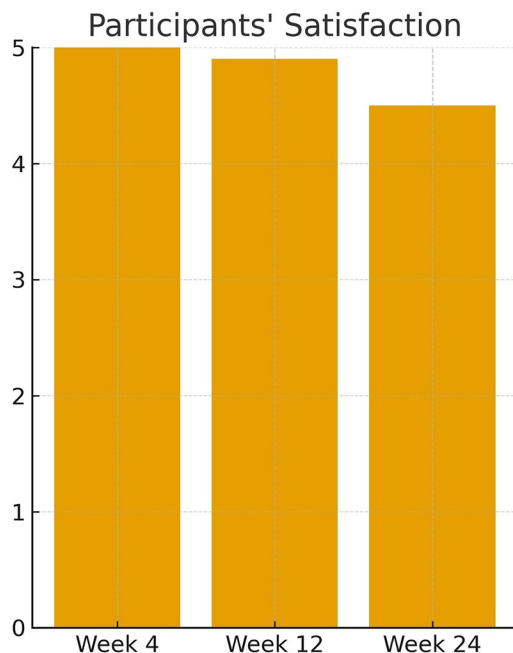


Figure 4. Participant satisfaction scores over time. Satisfaction was assessed using a 5-point Likert scale. Values represent mean ± SD.

Instrumental measurements

TEWL decreased from baseline (9.69 ± 3.07 g/m²/h) to week 12 (8.01 ± 2.44 ; $p = .0033$) and week 24 (8.23 ± 2.66 ; $p = .0267$) (Figure 5). Week 4 showed a downward trend (8.41 ± 3.23) but did not reach statistical significance ($p = .084$).

Corneometer values increased significantly from baseline (67.29 ± 11.33 AU) at all follow-up points: week 4 (72.37 ± 8.73 ; $p = .0128$), week 12 (75.07 ± 7.65 ; $p = .0125$), and week 24 (79.57 ± 6.48 ; $p = .001$) (Figure 6).

Cutometer analysis demonstrated significant, progressive improvements across all elasticity parameters after treatment. Overall viscoelasticity (R2) increased from baseline (49.11 ± 13.17) to 55.29 ± 12.88 at week 4 ($p = .0126$), 56.91 ± 12.37 at week 12 ($p = .0002$), and 62.13 ± 17.06 at week 24 ($p = .0007$). Net elasticity (R5) showed a similar pattern, rising from 37.44 ± 13.13 at baseline to 43.02 ± 15.75 at week 4 ($p = .0112$), 47.71 ± 15.77 at week 12 ($p = .0002$), and 57.02 ± 26.18 at week 24 ($p = .0023$). Biological elasticity (R7) improved steadily as well, increasing from 32.15 ± 10.13 at baseline to 34.49 ± 10.21 at week 4 ($p = .0409$), 37.07 ± 10.18 at week 12 ($p = .0008$), and 41.49 ± 11.86 at week 24 ($p = .0003$) (Figure 7).

Safety

No treatment-related serious adverse events occurred. Mild, transient swelling occurred in 3 participants and bruising in 1 participant; all events resolved spontaneously within several days without intervention.

Discussion

This clinical study demonstrated that an HA–PN hybrid filler was associated with consistent, sustained improvements in anteromedial cheek volume, hydration, barrier function, and biomechanical elasticity. Early, persistent reductions in MFVDS score from baseline to week 24 are consistent with the established performance of cross-linked HA fillers, which demonstrated improvements in volume restoration through their viscoelastic and hydrophilic properties (1–3).

Beyond volumization, HA is increasingly recognized for its biologic contributions to skin quality. A recent meta-analysis of 12 clinical trials demonstrated that HA injections significantly improve hydration and radiance, supporting its role as a functional agent in reversing cutaneous aging in addition to contour restoration (11). Although improvements in elasticity were not consistently demonstrated across all studies, HA's hygroscopic properties, promotion of keratinocyte differentiation, and modulation of extracellular matrix (ECM) organization contribute meaningfully to epidermal barrier homeostasis and dermal quality (5,6).

PN offers complementary regenerative mechanisms. By activating A2A adenosine receptors and supporting nucleotide salvage pathways, PN promotes fibroblast proliferation, angiogenesis, anti-inflammatory signaling, and ECM synthesis (7–9). Growing clinical evidence indicates that PN also contributes to soft-tissue restoration. Kim et al. reported successful treatment of iatrogenic facial fat atrophy with PN injections, demonstrating gradual, natural-appearing volumetric recovery through regenerative remodeling rather than mechanical lifting (12). Similarly, Noury et al. found that PN-based biostimulatory injectables improved tear trough contour, pigmentation, and skin smoothness without adverse events, reinforcing PN's capacity to enhance both structural and qualitative parameters even in anatomically delicate regions (13).

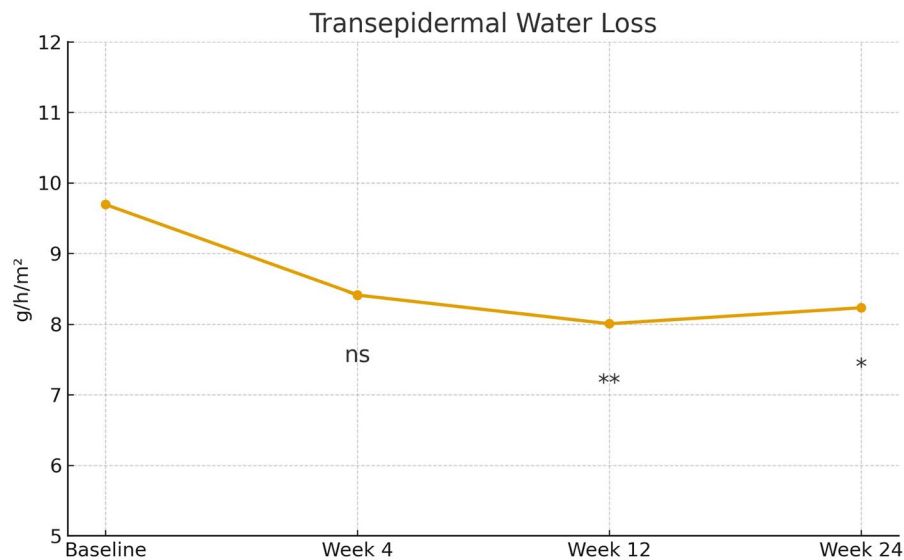


Figure 5. Transepidermal water loss (TEWL) measurements over time. TEWL was assessed at baseline and at weeks 4, 12, and 24 after treatment. A downward trend was observed at week 4 (8.41 ± 3.23) that did not reach statistical significance. Error bars indicate SD.

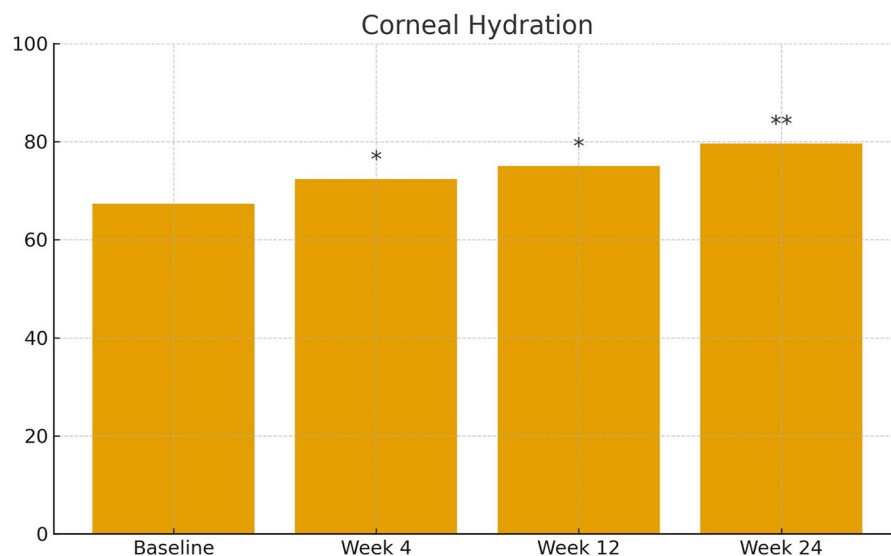


Figure 6. Skin hydration assessed by Corneometer. Measurements were obtained at baseline and during follow-up visits. Data are shown as mean $\pm$ SD.

Preclinical data further support mechanistic synergy between HA and PN. HA–PN complexes enhance collagen synthesis, improve dermal matrix organization, and reduce TRPV4-mediated inflammation compared with HA alone, suggesting additive or synergistic benefits (14). These mechanistic distinctions between HA and PN, including their complementary effects on hydration, volumization, ECM remodeling, and inflammation control, are summarized in Table 1.

The conceptual framework for interpreting such dual-action effects has recently been clarified. Yi et al. provided a comprehensive classification of ‘skin boosters,’ describing them as biologically active injectable agents that improve hydration, elasticity, texture, and overall skin quality through ECM remodeling and barrier reinforcement (15). Within this system, PN is categorized as a core regenerative biostimulator, whereas HA serves as a hydrating and structural agent. HA–PN hybrid fillers, therefore, fall within the class of multifunctional regenerative skin boosters designed to

address not only volume loss but also the qualitative deterioration that accompanies facial aging. This classification aligns closely with our observed improvements in TEWL, hydration, and elasticity.

Additional clinical literature on PN-containing or PN-primed filler protocols for nasolabial folds and periorbital rejuvenation supports parallel improvements in skin quality and aesthetic contour (10,16,17). Collectively, these findings provide an evidence-based explanation for the multidimensional improvements observed in this study and support a mechanistic model in which HA provides immediate contour and hydration and PN promotes progressive dermal regeneration.

The safety profile observed in this study is consistent with established clinical experience with HA and PN injectables. Only mild, transient swelling or bruising occurred in four participants, and no serious adverse events were reported. This safety profile parallels the favorable tolerability reported in previous PN-based and HA-based cosmetic studies (12,13,16).

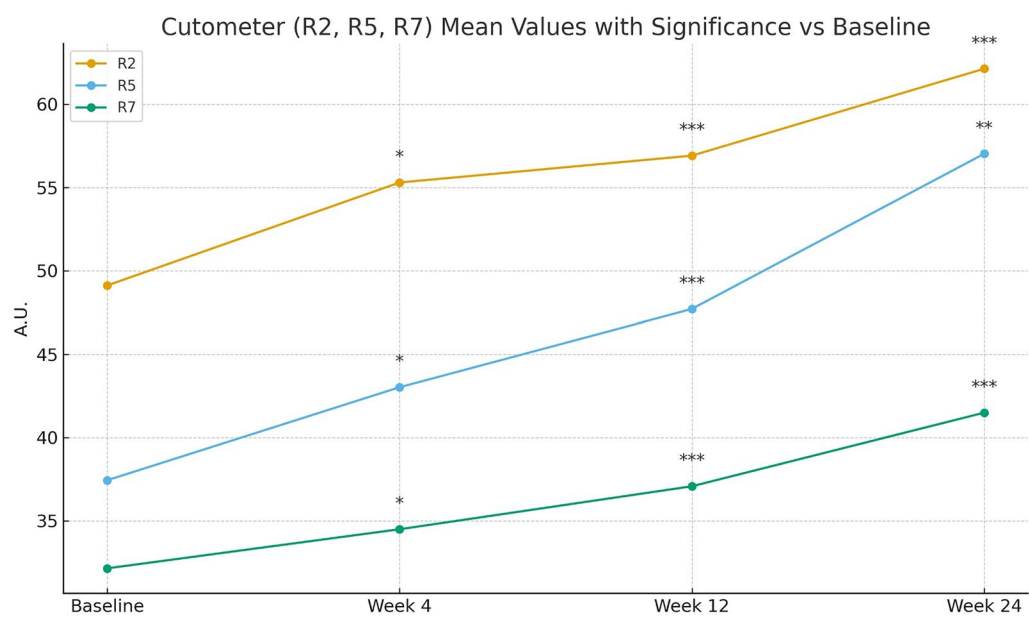


Figure 7. Cutometer analysis of skin elasticity (R2, R5, R7). Measurements were performed at baseline and at weeks 4, 12, and 24 after treatment. All parameters showed statistically significant improvement ($p < .05$). Values represent mean $\pm$ SD.

Table 1. Comparative roles of hyaluronic acid and polynucleotides in skin physiology and regeneration.

Category	Hyaluronic acid	Polynucleotides
Primary mechanism	Hydrophilic polymer with high water-binding capacity and a structural, space-filling scaffold (4–6,11)	DNA-derived polymer that activates the A2A receptor and nucleotide salvage pathways (7–9,17)
Main biological actions	- Increases hydration - Supports the ECM through the HA network - Provides immediate volumization via its viscoelastic gel (4–6,11)	- Modulates anti-inflammatory cytokines - Increases fibroblast proliferation - Enhances angiogenesis - Increases collagen and elastin synthesis (7–9,12–13,17)
Target skin layers	Primarily dermis (ECM) (4,5)	Dermis and subcutis (fibroblasts and microvasculature) (7–9,17)
Effect on barrier function	Improves TEWL through increased hydration and keratinocyte differentiation (11)	Reduces barrier disruption from inflammation and promotes repair (7–9,17)
Effect on ECM remodeling	Has limited direct collagen stimulation and provides a temporary framework (4–6)	Promotes strong ECM remodeling with increased type I collagen, elastin, and GAGs (7–9,12–14,17)
Volumizing effect	Immediate and strong because of gel viscoelasticity (4–6)	Provides minimal direct volume and acts via regeneration (12–14,17)
Durability	8–12 months, depending on cross-linking and area (4–6)	Progressive improvement over weeks with tissue-based durability (12–14,17)
Anti-inflammatory effects	Mild to moderate anti-inflammatory activity (12)	Strong anti-inflammatory activity mediated by the A2A receptor (7–9,17)
Clinical benefits	- Provides immediate contour correction - Improves hydration and radiance (4–6,11)	- Provides long-term improvement in skin quality - Promotes atrophy repair and enhances texture and elasticity (12–14,17)
Typical indications	Midface volume loss, facial contouring, and nasolabial folds (4–6)	Skin rejuvenation, atrophy repair, and periocular and other delicate areas (12–14,17)
Limitations	Degrades over time and has limited regenerative capacity (4–6)	Has a slower onset with no direct volumizing effect (12–14,17)

ECM, extracellular matrix; GAGs, glycosaminoglycans; TEWL, transepidermal water loss.

These findings should be interpreted in light of several limitations. First, the open-label, single-arm design without a control group precludes direct comparison with HA-only or PN-only treatments; thus, the individual contributions of each component and the presence of true synergy cannot be conclusively determined. Second, the absence of randomization or blinding in treatment administration introduces potential performance and assessment bias. Third, the small sample size limits statistical power and the generalizability of the findings. The study population consisted exclusively of Korean women, which may limit applicability to other demographic groups. Because this was an exploratory pilot study with a small sample size, no *a priori* power calculation was performed. Multiple statistical comparisons were conducted without adjustment for multiplicity; therefore, the reported *p*-values should be interpreted as exploratory and hypothesis-generating rather than confirmatory. Finally, imaging or histologic assessments were not performed, preventing direct visualization of ECM-level remodeling.

Overall, the HA–PN hybrid filler demonstrated durable volumizing effects accompanied by meaningful improvements in hydration, barrier function, and elasticity. These outcomes are consistent with the dual-action mechanistic framework described in recent literature and support the clinical utility of HA–PN hybrid formulations as comprehensive rejuvenation tools. Future randomized controlled studies comparing HA–PN hybrids with HA-only and PN-only injectables, supplemented by imaging or histologic correlates, will be valuable for establishing the distinct and combined contributions of HA and PN.

Acknowledgments

The author acknowledges support from the Technology Innovation Program (or Industrial Strategic Technology Development Program-Material and Component Technology Development Project [Heterogeneous Technology Convergence Type] [20024946, Development of Tissue

Regenerative Biosurgery Convergence Medical Products Using High-Functional Implantable Biomaterials]], funded by the Ministry of Trade, Industry and Energy (MOTIE, Korea).

Author contributions

The authors were responsible for all aspects of the study, including conceptualization, methodology, data collection and analysis, manuscript preparation, and final approval.

Ethical approval statement

This study was approved by the Institutional Review Board (IRB approval number 2406-021-604) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants before enrollment in the study.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Trial registration

This study was registered with the Clinical Research Information Service (CRIS), Korea (registration number KCT0011171; URL: <https://cris.nih.go.kr>).

Funding

This study was supported by a research grant from BMI KOREA CO., LTD. (Gyeonggi, Korea). The sponsor had no role in the study design, data collection, data analysis, data interpretation, or manuscript preparation.

Data availability statement

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

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