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# Supersonic Cryogenic Jet Delivery of Polynucleotides Compared With Manual Intradermal Injection

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**Background:** This study explores an alternative method of delivering polynucleotides (PNs) using a transdermal drug delivery device instead of traditional injection methods. These devices can deliver PNs in a noncontact manner and may offer several advantages over traditional injection techniques, including reduced pain and faster recovery time.

**Methods:** A clinical trial was conducted to compare the effectiveness of PN injections and transdermal drug delivery devices in 4 participants. Each participant received 3 treatments using the injection method on one side of the face and the transdermal drug delivery device on the other. The right hemiface was treated with cryogenic transdermal delivery (TargetCool), and the left hemiface was treated with manual intradermal injection. Outcomes were assessed through standardized photography and skin analysis, and participant satisfaction was examined using the Global Aesthetic Improvement Scale and visual analog scale.

**Results:** Treatment with the transdermal drug delivery device showed similar skin improvement to PN injection, with the advantage of less pain and a shorter recovery time. Skin density measurements using ultrasound showed that both methods were effective, but the transdermal drug delivery device provided slightly better skin density improvement in some cases.

**Conclusions:** Transdermal drug delivery devices are a safe and effective alternative to traditional PN injections, with similar skin improvement outcomes. *(Plast Reconstr Surg Glob Open 2026;14:e7509; doi: 10.1097/GOX.0000000000007509; Published online 17 February 2026.)*

## INTRODUCTION

Polynucleotides (PNs) are an advanced dermatologic treatment that targets skin regeneration and repair. They contain key components of DNA, which play an important role in maintaining the health and vitality of the skin. PNs stimulate the activity of fibroblasts, the cells that produce collagen and elastin, to induce skin regeneration and aid in wound healing and tissue regeneration. PNs have anti-inflammatory and antioxidant properties that have been shown to reduce wrinkles, improve skin elasticity, minimize pores, equalize skin tone, and increase skin hydration.

One of these products, Rejuran (PharmaResearch Inc., Korea), is derived from salmon sperm DNA and has skin regenerating, anti-inflammatory, and antioxidant properties. It has been shown to reduce wrinkles, improve skin elasticity, shrink pores, even out skin tone, and increase skin hydration. It can be used to treat fine lines, acne scars, and dark circles under the eyes due to its ability to improve the overall health of the skin.[1–5]

PN injections are administered using a very thin microneedle (typically 31G or smaller diameter) that is evenly injected into the dermal layer of the facial area. The

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injection points are arranged in a grid pattern across the facial area, with the spacing between each injection point at approximately 1–2 cm. This ensures that the product is distributed evenly across the skin. After the procedure, redness, swelling, and bruising may temporarily appear and require time to resolve.[6–9]

TargetCool is a medical device developed by Recens Medical, equipped with a transdermal drug delivery system platform technology that enables drug delivery and precision cooling therapy. This technology uses a high-velocity cryogenic microjet drug delivery method that delivers micronized cryogenic drug particles into superficial skin layers and converts drugs into microneedle-like ice particles that can penetrate the stratum corneum (Fig. 1). The thinner the needle, the less painful the procedure, and IceNeedling uses these thin needles to minimize pain during injection (Fig. 2). It provides immediate regenerative effects through direct absorption, and the lack of downtime has been shown to reduce inflammation caused by other cosmetic procedures.

## Takeaways

**Question:** Can polynucleotides (PNs) be effectively and safely delivered using a supersonic cryogenic system (TargetCool) as an alternative to intradermal injection?

**Findings:** In a split-face study of 4 patients, cryogenic jet delivery produced clinical results comparable to manual PN injection, with less pain and faster recovery. No significant differences were found in patient satisfaction or imaging parameters between the 2 techniques.

**Meaning:** Cryogenic transdermal PN delivery offers a promising noninvasive alternative to manual injection, providing similar rejuvenation outcomes with improved tolerability and reduced downtime.

## METHODS

This study was approved by the Korean Public Approved Research Foundation (KPIRB-2024-054). This pilot study enrolled 4 patients to compare and evaluate the effectiveness of 2 PN delivery methods. All participants had no significant medical history and presented with varying baseline skin conditions.

Each participant underwent 3 treatment sessions at 2-week intervals. The face was divided into right and left halves, with each side receiving a different treatment modality:

Right facial area (cryogenic transdermal delivery; TargetCool): A microneedle therapy system was first applied evenly, after which the same dose (1 mL) of Rejuran was delivered into the dermis using a noncontact cryogenic drug delivery device (TargetCool) (Fig. 3).

Left facial area (traditional intradermal injection method): A topical anesthetic cream was applied, followed by intradermal injection of 1 mL of PN product (Rejuran) using a syringe and 31G microneedle.

This split-face design allowed direct comparison of the clinical effects and patient-reported outcomes of each method. (**See Video 1 [online]**, which displays a clinical demonstration of cryogenic PN delivery using the TargetCool device, showing real-time application of a supersonic cryogenic microjet to the lateral midface and periorbital region with micronized ice particles penetrating the skin without needle contact. The video illustrates the noninvasive delivery process, uniform dermal dispersion, minimal discomfort, and the use of protective ocular shields; all patients provided written informed consent for publication.)

### Evaluation Method

Clinical outcomes were assessed through standardized digital photography, skin analysis, and ultrasound imaging.

#### *Ultrasound Evaluation*

A high-frequency ultrasound system (eg, 20-MHz linear probe) was used to measure dermal density and thickness at identical anatomical points on both facial halves. Measurements were taken at baseline, 1 month, and 3 months after the final treatment. All assessments were performed with the probe placed perpendicular to the skin surface, and images were captured in B-mode (Fig. 4). Skin density was calculated using the device's integrated software, ensuring reproducibility by maintaining consistent probe pressure and location during follow-up visits.

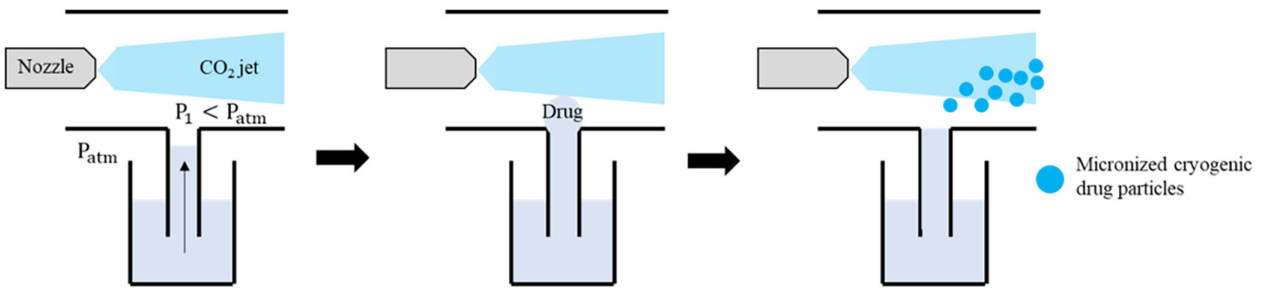


**Fig. 1.** Formation of micronized cryogenic drug particles during the cryogenic processing phase.

**Fig. 2.** Morphological characteristics of solidified cryogenic drug particles following micronization.

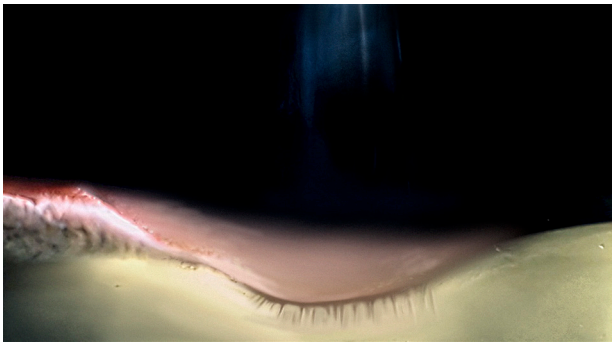

**Fig. 3.** High-speed camera imaging of transdermal penetration, demonstrating supersonic delivery of solid cryogenic drug particles.

For the cryogenic transdermal delivery, micronized PN ice particles traverse the stratum corneum and preferentially lodge within the upper to mid-dermis, producing multiple small intradermal foci. For the manual injection, despite an intradermal intent (31G), some aliquots may track into the immediate subdermis in areas with mobile skin, producing a shallow subdermal depot that can transiently compress the dermis on ultrasound.

### *Subjective Satisfaction*

Patients completed questionnaires, including the Global Aesthetic Improvement Scale (GAIS; 1 = worse; 2 = no change; 3 = improved; 4 = much improved; 5 = very much improved) and the visual analog scale (VAS; 1 = minimal pain; 5 = very painful). GAIS scores were also independently assessed by 2 experienced dermatologists blinded to treatment allocation.

### Statistical Analysis

All statistical analyses were performed using SPSS software (version 27.0; IBM Corp., Armonk, NY). Paired comparisons between the 2 treatment modalities (traditional injection versus cryogenic transdermal delivery) were conducted using the Wilcoxon signed-rank test. A 2-tailed *P* value of less than 0.05 was considered statistically significant.

## RESULTS

### Patient Selection and Eligibility Criteria

This pilot study included 4 adult patients (2 females, 2 males; age range 32–48 y) recruited from our clinic between March and April 2024. All participants provided written informed consent. The inclusion criteria were: (1) age between 20 and 60 years; (2) presence of visible signs of facial skin aging such as fine lines, decreased elasticity, or uneven texture; and (3) willingness to undergo both traditional injection and transdermal drug delivery on contralateral facial sides. The exclusion criteria were (1) history of hypersensitivity to salmon-derived products or components of the PN formulation; (2) active skin infection, inflammation, or dermatologic disease in the treatment area; (3) keloid tendency or poor wound healing; (4) pregnancy or lactation; (5) systemic illness or immunosuppression; and (6) cosmetic facial procedures within the preceding 6 months. Baseline demographic and skin condition data for all participants, including Fitzpatrick skin type, primary skin concerns, and relevant medical history, are summarized in Supplemental Digital Content 1. (**See table, Supplemental Digital Content 1**, which displays a baseline demographic and skin condition data for all participants, **https://links.lww.com/PRSGO/E671**.)

### Follow-up and Outcomes

The safety and efficacy of the new transdermal drug delivery device with the traditional injection methods were compared in clinical studies to determine the impact of each on skin regeneration and repair and to explore the potential of noninvasive treatment modalities. Clinician-rated improvement (GAIS) and pain (VAS) scores are summarized in Supplemental Digital Content 2. (**See table, Supplemental Digital Content 2**, which displays GAIS scores [described separately below] and VAS scores

[on a 5-point scale with 5 being very painful], **https://links.lww.com/PRSGO/E672**.)

**Ultrasound Skin Density Analysis**

We quantified dermal thickness (mm) by caliper and dermal density as normalized grayscale backscatter (0–255) within a 1-mm region of interest spanning the papillary–upper reticular dermis. Across participants, the cryogenic transdermal (right) side showed intradermal hypoechoic microblebs and a net increase in dermal density (eg, +8% and +18% in patients 2 and 3, respectively), whereas the needle (left) side more often displayed a thin hypoechoic band immediately beneath the dermis, consistent with superficial subcutaneous ("subdermal") deposition, with transient dermal thickness reduction consistent with mechanical compression (eg, −8% thickness at 1 mo in patient 1), followed by partial normalization by month 3.

Raw ultrasound density measurements at baseline and 3 months are summarized in Supplemental Digital Content 3. (**See table, Supplemental Digital Content 3**, which displays ultrasound examination results [skin density], **https://links.lww.com/PRSGO/E673**.)

***Change in Skin Density***

After cryogenic delivery, skin density on the right facial area increased by 8% and 18% in patients 2 and 3, respectively, and decreased by 4% in patient 1 (Table 1). In contrast, on the left facial area treated with the traditional injection method, density decreased or showed only a negligible increase across patients (−8% in patient 1; +3% and +4% in patients 2 and 3, respectively). Patient 4 showed no meaningful change on either side (Table 1).

Comparing the skin density on the right side of the face (base R) with the left side (base L) shows a *P* value of 1.000, indicating no significant difference. After 3 months, the comparison between the right facial area (3 mo R) and the left facial area (3 mo L) showed a *P* value of 0.109, which did not reach statistical significance ($P > 0.05$).

**General Satisfaction**

Detailed questionnaire results for subjective symptom improvement are summarized in Supplemental Digital Content 4. (**See table, Supplemental Digital Content 4**, which displays a questionnaire assessing subjective satisfaction with skin symptoms by the subjects, using a 5-point scale where 0 indicates no improvement and 5 indicates very much improved, **https://links.lww.com/PRSGO/E674**.)

The right facial area (cryogenic transdermal delivery; TargetCool) received scores of 2, 3, 1, and 2 (Fig. 5), whereas the left facial area (manual intradermal injection) received scores of 4, 3, 1, and 2 (Table 2). Overall, the left side showed higher satisfaction (**Supplemental Digital Content 3**, **https://links.lww.com/PRSGO/E673**).

For elasticity/tightening, the right side scored 2, 3, 1, and 1, whereas the left side scored 4, 3, 1, and 2, indicating better outcomes on the left. Skin texture results were similar, with the right side scoring 2, 3, 1, and 1, and the left side scoring 4, 3, 1, and 1, again favoring the left side. Skin tone, pigmentation, and radiance showed minimal differences, with scores of 1, 1, 1, and 2 on the right, and 1, 2, 1, and 3 on the left. For enlarged pores, the right side scored 2, 3, 1, and 1, whereas the left side scored 3,

**Table 1. Change in Skin Density (%) at 3 Months**

| Patient | Device Side (Right) | Injection Side (Left) |
|---|---|---|
| 1 | −4 | −8 |
| 2 | +8 | +3 |
| 3 | +18 | +4 |
| 4 | 0 | 0 |
| *P* | 0.109 | — |

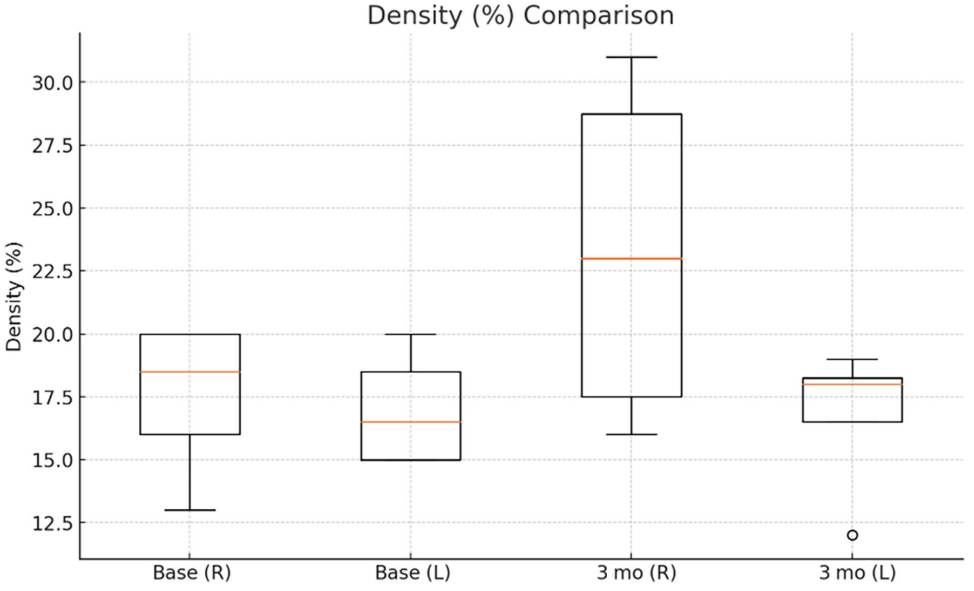


**Fig. 4.** Ultrasonographic assessment of skin density before and after treatment.

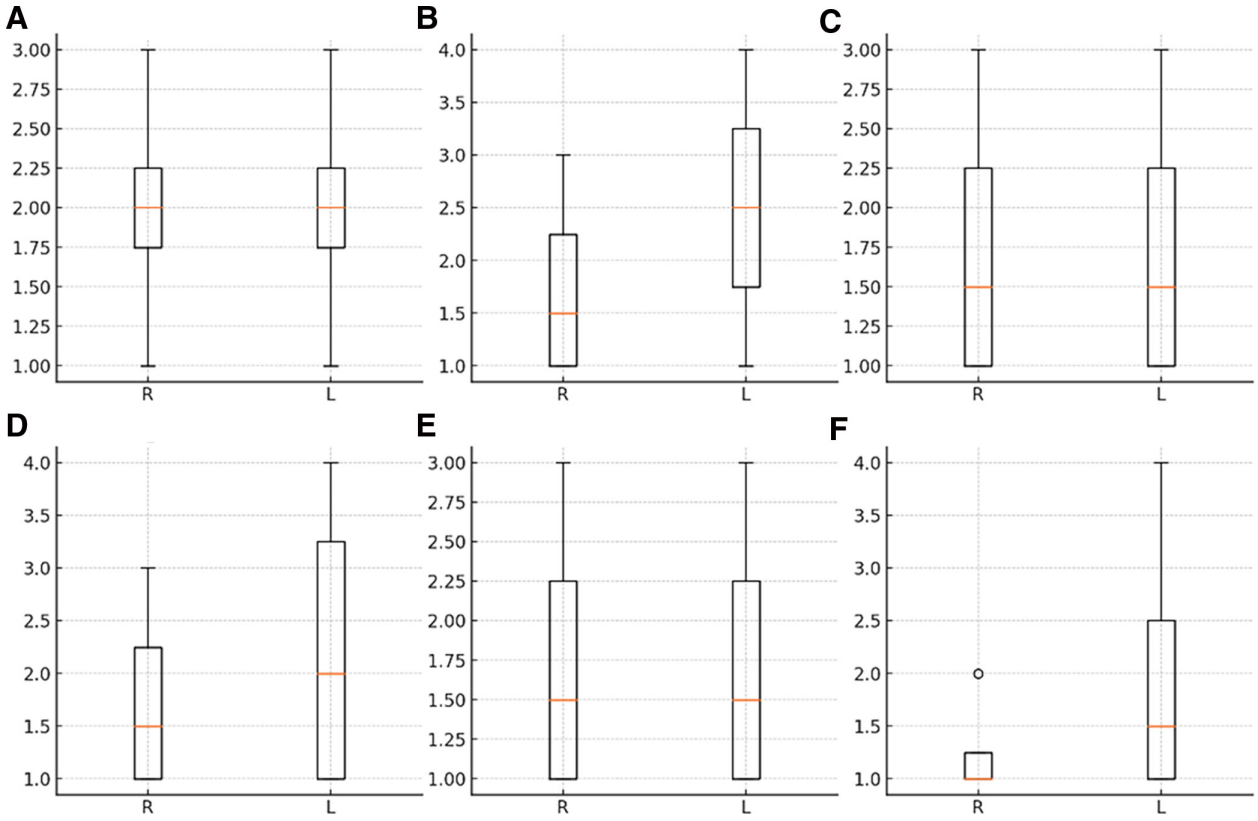


**Fig. 5.** Subjective patient-reported outcomes for skin symptom improvement, evaluated using a 5-point Likert scale (0 = no improvement; 5 = marked improvement). A, General satisfaction. B, Elasticity/tightening. C, Skin texture. D, Skin tone/pigmentations/radiance/glow. E, Enlarged pores. F, Skin redness/sensitivity.

**Table 2. Subjective Satisfaction Scores at 3 Months**

| Parameter | Patient 1 (R/L) | Patient 2 (R/L) | Patient 3 (R/L) | Patient 4 (R/L) | *P* |
|---|---|---|---|---|---|
| General satisfaction | 2/4 | 3/3 | 1/1 | 2/2 | 0.317 |
| Elasticity/tightening | 2/4 | 3/3 | 1/1 | 1/2 | 0.180 |
| Skin texture | 2/4 | 3/3 | 1/1 | 1/1 | 0.317 |
| Skin tone/pigmentation/radiance | 1/1 | 1/2 | 1/1 | 2/3 | 0.157 |
| Enlarged pores | 2/3 | 3/2 | 1/1 | 1/1 | 1.000 |
| Skin redness/sensitivity | 1/1 | 1/4 | 1/1 | 2/2 | 0.317 |

L, left side (injection); R, right side (device). Scores on a 0–5 scale; higher scores, greater improvement.

2, 1, and 1, with the right side showing a slight advantage. Skin redness and sensitivity scores were 1, 1, 1, and 2 on the right, and 1, 4, 1, and 2 on the left, slightly favoring the left.

The Wilcoxon signed-rank test yielded *P* values of 0.317 for general satisfaction, 0.180 for elasticity/tightening, 0.317 for skin texture, 0.157 for skin tone/pigmentation/radiance, 1.000 for enlarged pores, and 0.317 for skin redness/sensitivity. None of these differences reached statistical significance ($P > 0.05$). All these results were not significantly different ($P > 0.05$), suggesting that there was no significant difference in subjective satisfaction between the 2 procedures Table 2.

In conclusion, subjective satisfaction tended to be higher on the right (injection) side, although differences were not statistically significant. The left (cryogenic) side showed comparable outcomes in several items (Fig. 6).

## DISCUSSION

The divergence in early dermal thickness (transient thinning on the needle side versus preservation/relative increase on the cryogenic side) can plausibly be explained by subdermal bolus–related compression after needle injection versus intradermal lattice-like dispersion with cryogenic delivery. This study showed that PN treatments using a transdermal drug delivery device can provide potential benefits similar to those of traditional injection methods, including reduced pain, shorter recovery time, lifting effects, and skin improvement. Although previous studies have demonstrated the skin rejuvenating effects

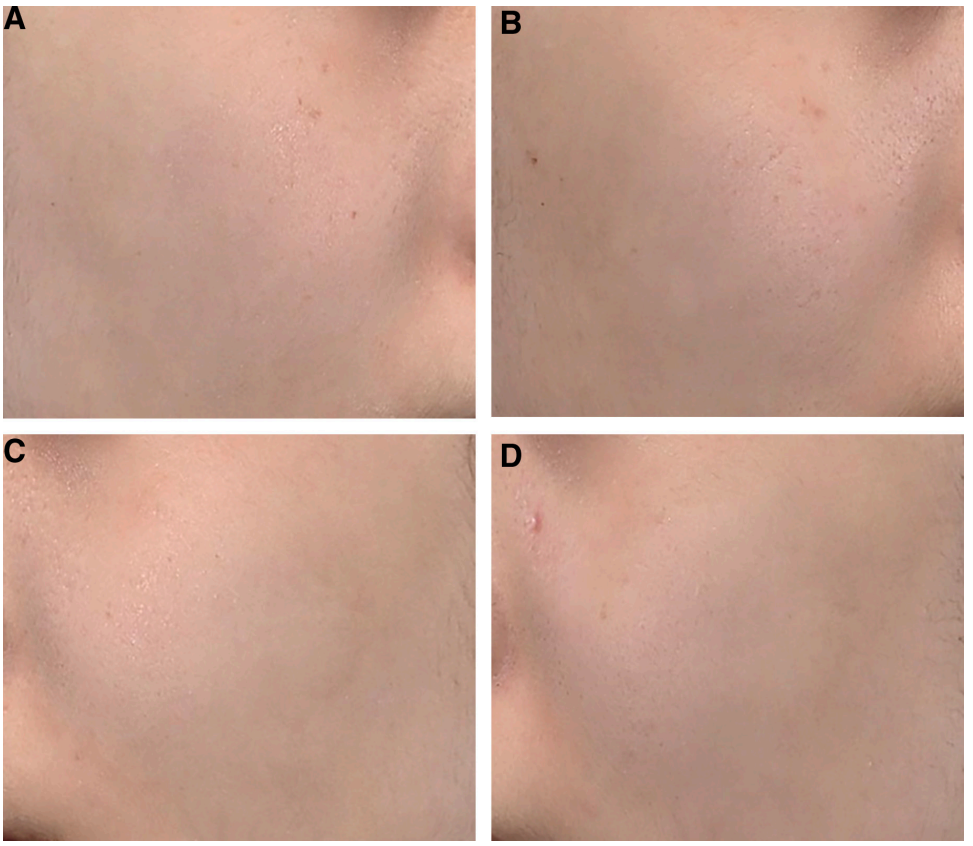


**Fig. 6.** Clinical comparison of facial skin appearance at baseline and 3 months after treatment with two injection methods. Standardized clinical photographs comparing baseline appearance (A, C) with outcomes at 3 months posttreatment (B, D).

of PNs, this study showed that transdermal drug delivery devices have the potential to deliver these benefits in a noninvasive manner.

In terms of the potential impact of cryogenic exposure on the efficacy of PNs, previous studies have demonstrated that PN-based products maintain their molecular integrity and biological activity when exposed to low temperatures, provided that storage and handling adhere to established stability protocols. Kim et al[10] reported that highly purified PNs derived from salmon DNA are stable under freezing conditions and retain their structural and functional properties, including fibroblast activation and collagen synthesis. The TargetCool system uses rapid cryogenic delivery, in which PNs are transformed into microcrystalline ice particles and delivered within milliseconds, minimizing any prolonged exposure that could lead to degradation. Therefore, it is unlikely that the cryogenic process used in this study compromised the chemical composition or regenerative capacity of the PN product.

From a clinical standpoint, cryogenic delivery of PNs offers several potential advantages that may broaden its application in aesthetic medicine. The contactless nature of the technique is particularly appealing for needle-averse patients or those with heightened injection anxiety, expanding access to regenerative treatments for a wider patient population. Additionally, the minimal discomfort and lack of downtime facilitate integration into multimodal rejuvenation protocols, such as in combination with energy-based devices or other injectable treatments, without significantly disrupting workflow or patient schedules. By reducing procedure time, minimizing anesthesia requirements, and potentially lowering the incidence of procedure-related erythema or bruising, cryogenic delivery can streamline practice operations while maintaining comparable clinical outcomes to traditional injection methods. These features suggest that cryogenic drug delivery could play a valuable role as both a standalone treatment option and an adjunctive tool in comprehensive facial rejuvenation strategies. The contactless or noninvasive approach of transdermal drug delivery may be especially effective for patients who have a fear of or discomfort with injections, as it improves the absorption of and effectiveness of PNs while making the treatment more convenient and accessible. Despite the limitations of this study's small sample size and short follow-up period, it suggests that transdermal drug delivery devices are a promising alternative to injection procedures. Larger and longer-term follow-up studies are needed to confirm these findings further. Transdermal drug delivery devices may be considered a safe and effective option to injection procedures for patients seeking PN therapy, providing more patients with a range of treatment options.

## CONCLUSIONS

In the present study, no adverse events such as persistent erythema, infection, granuloma formation, or delayed hypersensitivity were observed during the treatment course or follow-up period, supporting the safety profile of cryogenic PN delivery. These findings align with previous reports on similar cryogenic drug delivery devices, which have demonstrated minimal procedural complications and favorable tolerability profiles when operated within recommended parameters.[11] Furthermore, the comparable clinical improvement observed between cryogenic delivery and traditional injection, combined with the absence of significant adverse effects, reinforces its potential as an effective and well-tolerated alternative for skin rejuvenation. This is consistent with existing literature indicating that the rapid cooling and microneedle-like penetration of ice particles in cryogenic delivery do not compromise the therapeutic efficacy of bioactive agents.[11,12]

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## DISCLOSURE

*The authors have no financial interest to declare in relation to the content of this article.*

## ETHICAL APPROVAL

*This study was approved by the Korean Public Approved Research Foundation (KPIRB-2024-054), and all participants provided written informed consent in accordance with the Declaration of Helsinki.*

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