



Exploratory Study on 35 kDa Hyaluronan with Microneedling for Skin Concerns: A Series of 16 Cases

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Abstract

Purpose: This study aims to evaluate the short-term effectiveness and safety of 35 kDa low molecular weight Hyaluronan (HA35) combined with negative pressure microneedling technology in improving skin hydration, brightness, and inflammation within a four-week observation period.

Patients and methods: Sixteen subjects with skin issues—including dryness, roughness, dull complexion, and enlarged pores—were recruited, with seven participants also presenting with chronic skin inflammation. Each subject received a single treatment using DermaShine PRO microneedling combined with HA35. Skin condition was evaluated 20 minutes post-treatment and during follow-up using a skin analyzer, an improved Visual Analog Scale (VAS), and patient satisfaction surveys.

Results: The results demonstrated significant improvement in skin dryness and roughness ($P<0.01$) and increased brightness ($P<0.05$) within 20 minutes of treatment. Subjects with chronic inflammation showed a marked reduction in inflammation hardness and erythema ($P<0.01$). The treatment effect persisted for over one month, with 100% of participants reporting satisfaction during the follow-up period. No adverse reactions related to the procedure or product were observed throughout the study.

Conclusion: Negative pressure microneedling combined with HA35 offers an effective, non-pharmaceutical approach for improving skin hydration, brightness, and mild to moderate inflammation within a short-term period. This treatment demonstrates sustained effects over the four-week observation period and maintains high patient satisfaction. Given its safety and non-invasive nature, it represents a promising option for aesthetic dermatology, with potential for further optimization in future studies.

Introduction

Skin issues, often categorized as sub-healthy conditions, manifest clinically through symptoms such as dryness, dull complexion, enlarged pores, and acne¹. In more severe cases, these cosmetic concerns can escalate into chronic skin inflammation, presenting as pigmentation, persistent redness, and itching². These issues, whether cosmetic or inflammatory, significantly impact individuals' quality of life and prompt them to seek treatment^{3,4}. Cosmetic issues like roughness and dullness are typically managed through home remedies or aesthetic treatments, including hydration masks, collagen infusions, and hyaluronic acid injections^{5,6}. In contrast, chronic skin inflammation requires medical intervention, often involving antibacterial drugs or corticosteroids, which can lead to higher costs, longer treatment durations, and the need for multiple treatment strategies⁷. While current aesthetic treatments and

pharmaceutical interventions offer some relief, they are often associated with limitations. For example, long-term use of corticosteroids may lead to skin thinning and other side effects⁴. Furthermore, injections with high molecular weight hyaluronan (HA) and collagen, though effective for wrinkle reduction and dermal filling, often cause adverse reactions like redness, pain, and local inflammation⁸. The need for non-pharmaceutical interventions that address both cosmetic concerns and inflammation is therefore increasingly evident.

Microneedling technology has emerged as a promising solution for improving various skin conditions⁹⁻¹³. Originally introduced by Henry and colleagues in 1998 for transdermal drug delivery, microneedling has evolved significantly over the past two decades¹⁴. The integration of negative pressure technology, such as that used in South Korea's DermaShine PRO device, has improved treatment precision by combining microneedling with automated hydration delivery⁹⁻¹³. Unlike traditional injections, negative pressure microneedling devices can deliver skincare agents deeper into the dermis with minimal discomfort, reducing the risk of adverse reactions.

Although high molecular weight hyaluronan has shown immunosuppressive and anti-inflammatory properties, its large molecular size limits tissue permeability, restricting its use to surface-level treatments. Our research focuses on 35 kDa hyaluronan fragments (HA35), a low molecular weight version produced through enzymatic cleavage of high molecular weight HA^{15,16}. Studies have demonstrated that HA35 not only has enhanced tissue penetration but also exhibits anti-inflammatory properties and promotes wound healing in both cellular and animal models¹⁵⁻¹⁷. These characteristics make HA35 a promising candidate for non-pharmaceutical skin treatments¹⁸. This study serves as a proof-of-concept investigation focusing on the short-term safety and effectiveness of HA35 in improving skin hydration, brightness, and mild to moderate inflammation. By combining HA35 with negative pressure microneedling, we aim to explore a novel, minimally invasive approach that provides rapid and sustained improvements in skin quality. Our goal is to provide preliminary evidence supporting the feasibility and potential benefits of this treatment within a four-week observation period, laying the groundwork for future clinical applications and larger-scale studies.

Material and methods

Ethical Statement

This study was conducted at the Department of Dermatology, Changchun Jiahe Hospital between January 2024 and April 2024. The study was approved by the Ethics Committee of Changchun Jiahe Hospital on January, 2024 (approval number: ccjhwk/2024/01), in accordance with the Declaration of Helsinki. All participants provided

informed consent, including permission for image use in publication, and voluntarily underwent treatment using the DermaShine PRO microneedling device combined with HA35.

Inclusion Criteria

① Aged 18–65 years; ② Skin issues such as dryness, dull complexion, enlarged pores, or excessive oiliness, with symptoms persisting for at least 3 months. Individuals may not have experienced symptom improvement after attempting standard cosmetic treatments (e.g., moisturizers, serums, or salon facials); ③ Subjects experiencing persistent symptoms such as itching, redness, swelling, or pain for more than 6 weeks, diagnosed by a dermatologist; ④ Capable of adhering to study protocols and providing independent judgment.

Exclusion Criteria

① Pregnant or lactating women; ② Individuals with psychological or psychiatric disorders; ③ Subjects with irregular lifestyles (e.g., excessive drinking or overeating); ④ Allergies to hyaluronan or keloid formation tendencies; ⑤ Skin issues diagnosed as caused by endocrine disorders; ⑥ Individuals receiving other injection or topical treatments concurrently; ⑦ Participants with low platelet counts or significant anemia.

Product Description and Procedure

The treatment involved a mixture of hyaluronidase injection (1500 units/vial, H31022111, SPH No. 1 Biochemical & Pharmaceutical Co., Ltd., China) and hyaluronan injection (10 mg/mL, H20174089, Shanghai Haohai Biological Technology Co., Ltd., China). The mixture was pre-prepared in a sterile syringe, resulting in a 2.5 mL viscous liquid for use with the DermaShine PRO negative pressure microneedling device (Derma Shine Co., Ltd., Korea).

Participants lay supine (face up) or prone (face down) depending on the treatment area (e.g., face, neck, or upper back). The dermatologist cleansed the target area before treatment, and compound lidocaine cream (H20063466; Beijing Ziguang Pharmaceutical Co., Ltd., China) was applied to the site for 30 minutes to ensure adequate anesthesia. A 2.5 mL solution of HA35 was distributed proportionately among the selected injection sites. Face: 10–12 injections (about 0.25 mL per site). Neck and back: 5–7 injections per inflamed area, ensuring the product targeted localized inflammation. The HA35 solution was injected intradermally using the DermaShine PRO microneedling device at a depth of 1.0–1.5 mm. If multiple areas were treated, each area received proportionate doses based on its size and condition. Injections targeted both general skin issues (e.g., dryness or dullness) and localized

inflammation (e.g., erythema, hardness, or swelling). Following the injection, a cold revitalizing HA35 mask (25 mL, Qingdao Huinuode Biotechnology Co., Ltd., China) was applied to the treated area for 20 minutes to soothe the skin. Participants were then monitored for 30 minutes to observe any potential adverse reactions, such as redness, swelling, or discomfort.

Efficacy Evaluation

Photography and Instrument Measurements

High-resolution digital photographs were taken using a Canon EOS 5D Mark IV camera (30.4 MP) with a 50mm fixed lens, ensuring consistent lighting and a fixed distance of 50 cm between the camera and the subject. Photographs were captured before treatment and at 20 minutes, 1 hour, 6 hours, and 24 hours post-treatment to document visible changes in skin condition. The room lighting was standardized with 4000K LED light sources to avoid shadows and color distortions.

Skin moisture content was measured with the SHP88 skin analyzer (Courage+Khazaka, Germany) at three predefined injection points within the treatment area, with the mean value of these readings recorded. The analyzer was calibrated according to the manufacturer's instructions before each use to ensure measurement accuracy. Results were expressed as hydration percentage changes over time.

VAS and Scoring Consistency

Skin improvement was assessed using an 11-point Visual Analog Scale (VAS) by a dermatologist who was not involved in the treatment to reduce bias¹⁹. The assessment criteria included skin dryness, smoothness, pore size, and erythema severity, where a score of 0 indicated healthy, unaffected skin, and 10 represented the most severe state (e.g., extremely dry, large pores, rubber-like hardened skin). A detailed scoring rubric ensured consistency among evaluators.

Improvement Calculation

Improvement was calculated using two formulas, depending on the baseline and outcome scores: Improvement Rate = [(Pre-treatment Score - Post-treatment Score) / Pre-treatment Score] × 100%²⁰; Alternative Formula = [(Post-treatment Score - Pre-treatment Score) / (10 - Pre-treatment Score)] × 100%²¹; 100% improvement indicated a complete resolution of the condition; 60–99% was considered significant improvement; 25–59% represented moderate improvement, and <25% was considered ineffective.

Follow-up and Satisfaction Assessment

Participants were followed up at 1 week, 2 weeks, and 4 weeks post-treatment to assess treatment durability. During these follow-ups, participants rated their satisfaction using

an 11-point Numerical Rating Scale (NRS), where 0 = least satisfied and 10 = most satisfied.

Safety Evaluation

Participants were monitored for adverse reactions both during treatment and at all follow-up visits. Potential side effects associated with microneedling, such as pain, nausea, redness, swelling, itching, or localized inflammation, were recorded. To minimize these risks, the treatment protocol included cold revitalizing mask. Any reported discomfort was evaluated immediately, and subjects were observed for 30 minutes post-treatment for immediate reactions.

Follow-up assessments were conducted at 1 week, 2 weeks, and 4 weeks post-treatment, and any late-onset side effects were documented. However, no serious adverse events (such as infections, persistent swelling, or allergic reactions) were reported throughout the study period.

Statistical Analysis

Statistical data analysis was performed using SPSS 24.0 (IBM Corp., USA). Quantitative data were expressed as mean ± standard deviation ($\bar{X} \pm s$), and paired t-tests were used to compare pre-treatment and post-treatment values. Categorical data were expressed as percentages (%). A p-value <0.05 was considered statistically significant.

Results

Baseline Demographics and Clinical Characteristics

A total of sixteen participants (aged 22–55 years; mean age 42 ± 11) completed the treatment and follow-up. The most common skin concerns among participants included dryness, roughness, dull complexion, and enlarged pores, which were present on the face, neck, and back. Seven participants exhibited chronic inflammation-related symptoms such as erythema, skin thickness, and firmness, which were confined to the neck and back areas (*Table 1*). These characteristics were carefully documented at baseline and compared against post-treatment outcomes to assess the efficacy of the treatment.

Table 1: Baseline Demographics and Clinical Characteristics of the Patients

Characteristics		Number of Cases (%)
Gender	Female	11(68.75)
	Male	5(31.25)
Age (year)	18~30	2(12.5)
	31~45	8(50)
	46~65	6(37.5)
Location of skin problems	Located on face	9(56.25)
	Located on back	4(25)
	Located on neck	3(18.75)
Type of skin problems	Inflammatory skin	7(43.75)
	Non-inflammatory skin	9(56.25)

Skin Moisture Content

The skin moisture content at various time points post-treatment was measured in all 16 participants. These measurements were taken before treatment and at intervals of 20 minutes, 1 hour, 6 hours, and 24 hours after treatment (Figure 1). Post-treatment hydration levels showed significant improvement at each time point. The baseline skin moisture content averaged 35.63 ± 11.09 , and this increased to 39.52 ± 11.52 at 20 minutes ($P < 0.001$), 41.24 ± 10.90 at 1 hour, 41.59 ± 10.33 at 6 hours, and 41.58 ± 10.25 at 24 hours ($P < 0.0001$). These results highlight a marked and sustained increase in skin hydration post-treatment. Consistent improvements were observed across all three predefined injection points for each participant, suggesting that the treatment was effective in promoting skin moisture across different facial and body areas.

Clinical Efficacy

To better understand the clinical impact of the treatment, Visual Analog Scale (VAS) scores were compared to the hydration levels obtained from the SHP88 analyzer, providing a correlation between subjective assessments and instrumental measurements. Improvements in hydration were strongly associated with reductions in dryness scores, indicating that the treatment effectively alleviated skin dryness. Skin roughness scores showed a significant decrease, dropping from 5.81 ± 1.11 before treatment to 4.81 ± 0.91 within 20 minutes post-treatment (Figure 2A, $P < 0.01$). In terms of skin brightness, whiteness scores increased from 3.63 ± 1.45 pre-treatment to 4.19 ± 1.22 at 1 hour post-treatment, which was statistically significant (Figure 2B, $P < 0.05$).

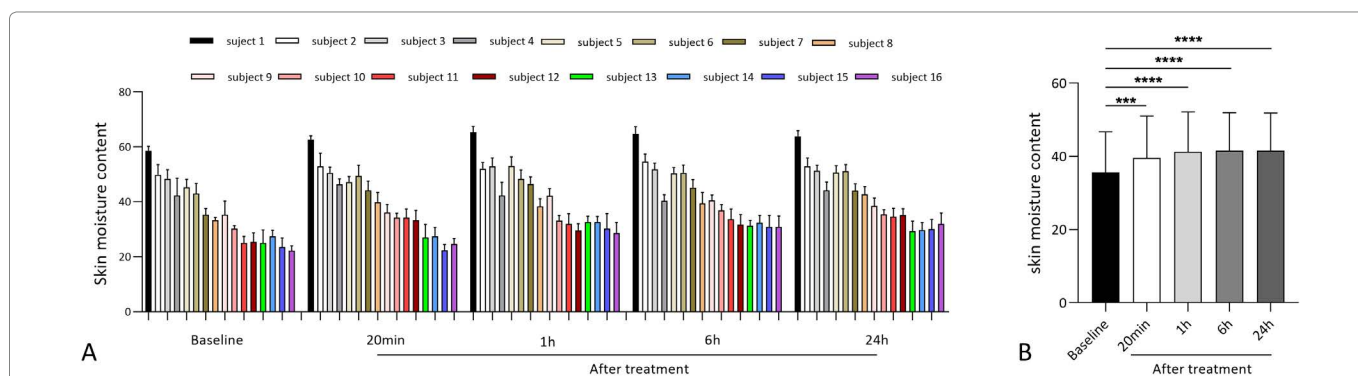


Figure 1: Skin moisture content at different times after injection.

Notes: (A) Measurement values of skin moisture for individual subjects; (B) Average skin moisture values for all subjects at different times.

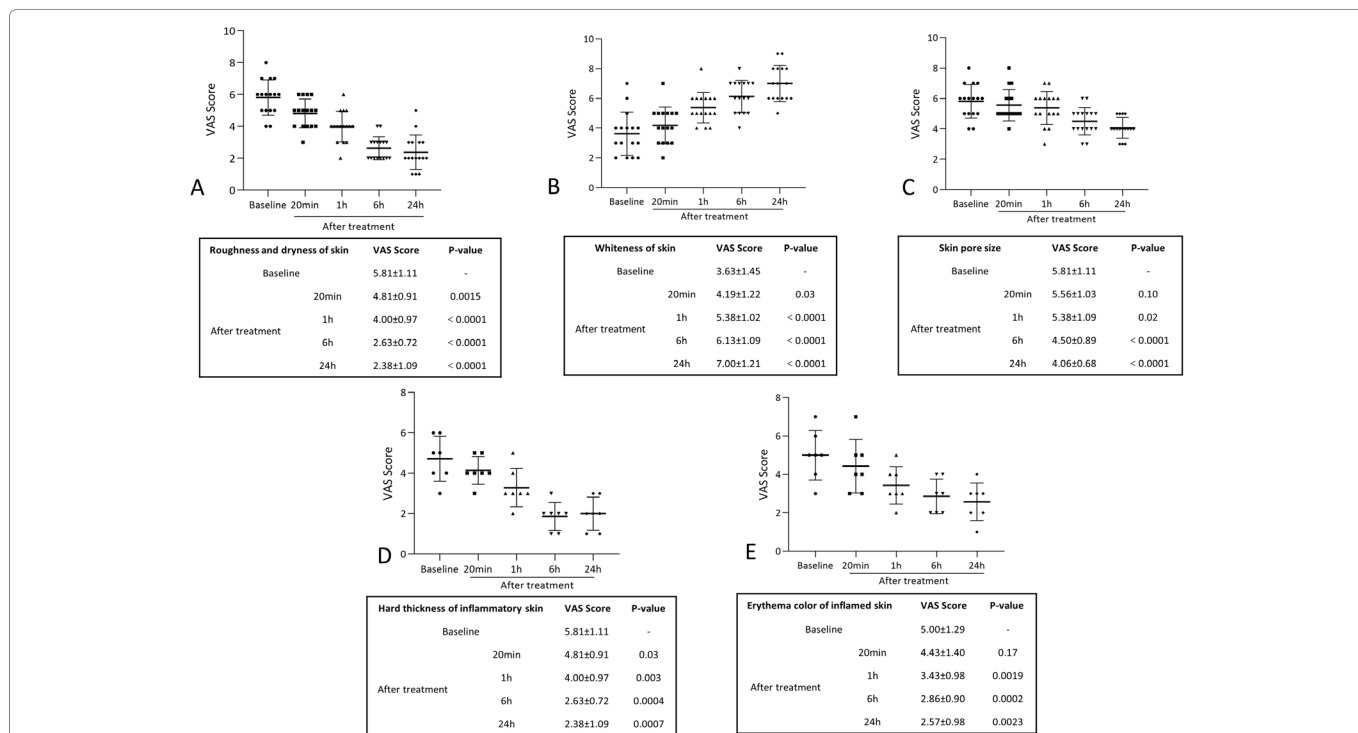


Figure 2: Evaluation scale scores at different times before and after treatment.

Notes: (A) Skin roughness and dryness; (B) Skin brightness; (C) Pore size; (D) Skin hardness and thickness; (E) Erythema.

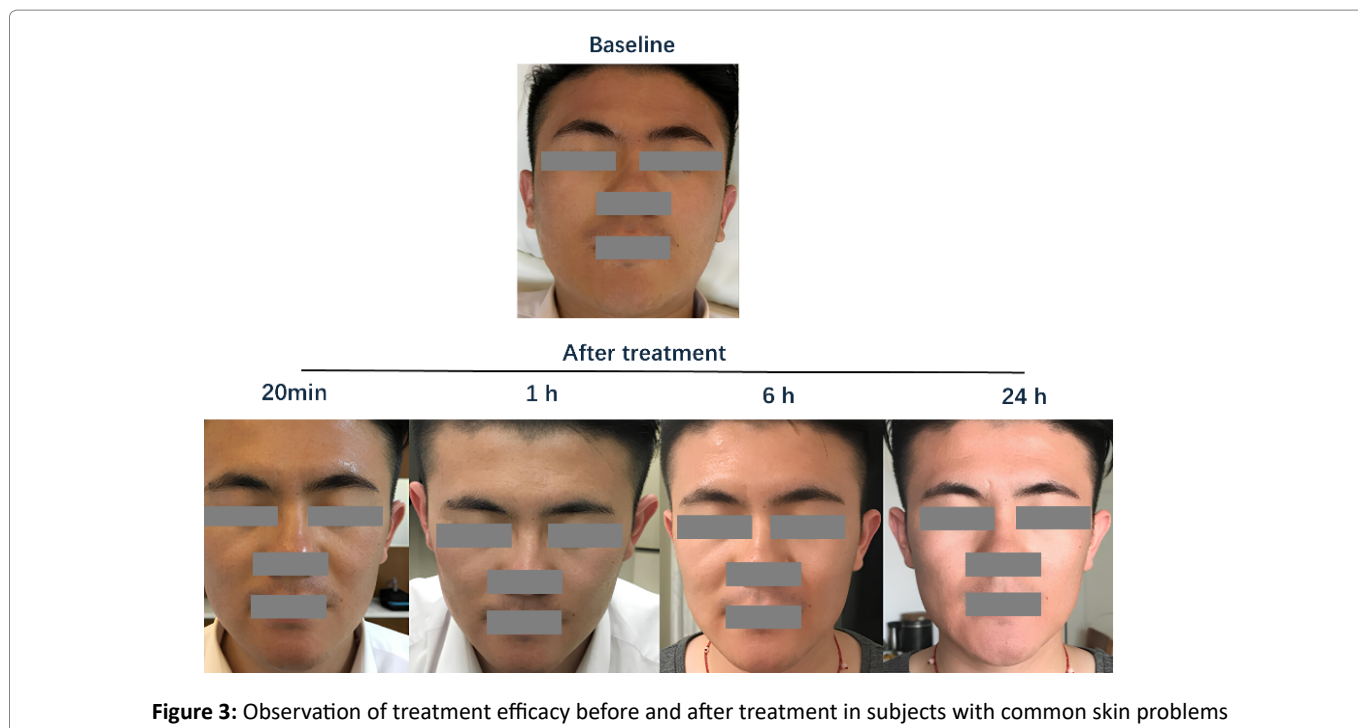


Figure 3: Observation of treatment efficacy before and after treatment in subjects with common skin problems

Pore size showed a gradual improvement over time, with significant reductions starting at 1 hour and continuing through to 24 hours (Figure 2C). This gradual yet sustained reduction in pore size indicates that the treatment has a lasting effect on skin texture. In participants presenting with inflammatory symptoms, significant improvements in thickness and hardness scores were seen as early as 20 minutes post-treatment ($P < 0.05$), while erythema severity showed more pronounced improvement at 1 hour (Figures 2D, 2E, $P < 0.01$). High-resolution photographic images in Figure 3 further confirmed these changes in subjects with common skin problems. The images showed a visible reduction in erythema and an improvement in overall skin brightness, suggesting a healthier and more even skin tone. These effects became more apparent over the 24-hour period following treatment, highlighting its positive impact on skin quality. Figure 4 documented similar improvements in subjects with chronic skin inflammation on the neck and back. The images revealed a noticeable reduction in erythema and irritation, along with enhanced skin brightness. These improvements were especially evident within the first 24 hours, indicating that the treatment effectively alleviates inflammation and promotes better skin condition in affected areas.

Clinical Improvement Rate and Satisfaction

Improvement rates based on VAS scores revealed progressive skin recovery, which was consistent across all participants (Table 2). At 1 hour post-treatment, most subjects reported moderate to significant improvements in skin texture and inflammation. Pore size improvement was more noticeable at 24 hours, further supporting the

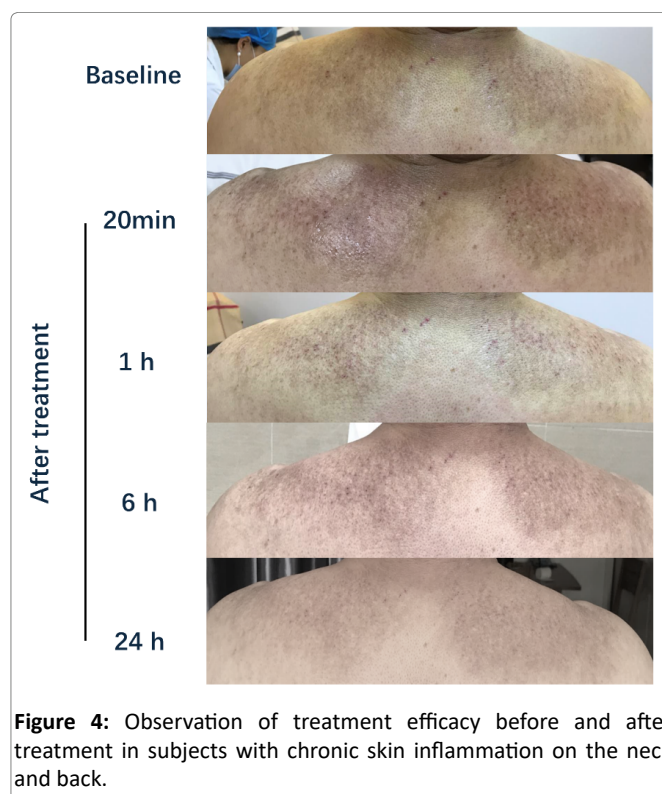


Figure 4: Observation of treatment efficacy before and after treatment in subjects with chronic skin inflammation on the neck and back.

delayed yet sustained impact of the treatment. Satisfaction scores were high, with peak satisfaction observed at 1 and 2 weeks post-treatment. Specifically, 62.5% of participants reported being satisfied, and 31.25% reported being very satisfied at 2 weeks. By 4 weeks, there was a slight decline in satisfaction, which was attributed to partial recurrence of symptoms, though the treatment effects were still

Table 2: Number and proportion of subjects with improved skin conditions after treatment

Time	Assessment Index	Roughness and dryness of skin	Whitiness of skin	Skin pore size	Hard thickness of inflammation	Erythema color of inflamed skin
20min	Significantly effective	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
	Effective	5(31.25%)	2(12.5%)	0(0%)	1(11.1%)	1(11.1%)
	Invalid	11(68.75%)	14(87.5%)	16(100%)	8(88.9%)	8(88.9%)
1h	Significantly effective	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
	Effective	10(62.5%)	11(68.75%)	1(6.25%)	6(66.7%)	6(66.7%)
	Invalid	6(37.5%)	5(31.25%)	15(93.75%)	3(33.3%)	3(33.3%)
6h	Significantly effective	7(43.75%)	1(6.25%)	0(0%)	7(77.8%)	1(11.1%)
	Effective	8(50%)	11(68.75%)	7(43.75%)	2(22.2%)	8(88.9%)
	Invalid	1(6.25%)	4(25%)	9(56.25%)	0(0%)	0(0%)
24h	Significantly effective	11(68.75%)	6(37.5%)	0(0%)	4(44.4%)	2(22.2%)
	Effective	5(31.25%)	9(56.25%)	10(62.5%)	5(55.6%)	5(55.6%)
	Invalid	0(0%)	1(6.25%)	6(37.5%)	0(0%)	2(22.2%)

Notes: Improvement rate of 100% is considered a cure, >60% is significant effect, 25-60% is effective, and <25% is ineffective.

Table 3: Subject satisfaction and satisfaction scores with skin condition before and after treatment

Index		Before treatment	1 week after treatment	2 weeks after treatment	4 weeks after treatment
Satisfaction level (Number)	Most dissatisfied (0 score)	3	0	0	0
	Dissatisfied (1-3 score)	12	0	0	0
	Satisfied (4-6 score)	1	10	13	15
	Very satisfied (7-9 score)	0	5	3	1
	Extremely satisfied(10 score)	0	1	0	0
Satisfaction scores		2.8±01.2	6.3±1.3	5.9±1.1	4.9±1.0
p-value		-	p<0.0001	p<0.0001	p<0.0001

clearly visible at the time of the follow-up. Despite this, all participants expressed a willingness to undergo future treatments, indicating a strong level of overall satisfaction (Table 3).

Adverse Reactions and Safety

No severe adverse events were reported during the study period. The most common side effects included temporary redness, mild swelling, and mild pain, all of which resolved within 24 hours post-treatment. These minor reactions were in line with what is typically expected from treatments involving hyaluronic acid injections. Importantly, participants did not experience the persistent swelling often associated with high molecular weight hyaluronan, underscoring the superior safety and tolerability of HA35 injections in this cohort.

Additionally, post-treatment cold revitalizing masks were used to help minimize discomfort during and after the procedure, further enhancing the overall treatment experience. No infections, allergic reactions, or other serious complications were observed throughout the study or during the follow-up period, confirming that the treatment was safe and well-tolerated by all participants.

Discussion

This study demonstrates that HA35 combined with

negative pressure microneedling significantly improves skin hydration, brightness, and inflammatory symptoms within 24 hours, with effects lasting up to four weeks. These findings provide preliminary evidence that HA35 holds strong potential as an alternative, non-pharmaceutical treatment for both cosmetic and inflammatory skin issues, addressing a key gap in current therapeutic options. The improvements observed—such as enhanced hydration, smoother texture, reduced erythema, and overall skin vitality—are indicative of HA35’s potential as an effective treatment option for a broad range of dermatological concerns, including both aesthetic and clinical conditions.

High molecular weight HA, traditionally used for dermal filling and skin hydration, has well-established benefits, but its use in clinical settings is often hampered by limited tissue penetration due to its large molecular size^{10,12,18}. This restriction prevents HA from reaching deeper skin layers where it can most effectively address chronic inflammation or promote more substantial skin rejuvenation^{22,23}. Additionally, high molecular weight HA, while beneficial for superficial hydration and anti-aging, is often associated with side effects like pain, redness, and swelling after injection²⁴. In contrast, our study shows that HA35, a low molecular weight fragment, overcomes these limitations by demonstrating enhanced permeability, rapid anti-inflammatory action, and the ability to promote

tissue healing¹⁵⁻¹⁸. This is consistent with prior research showing that low molecular weight hyaluronan fragments are more effective in modulating inflammation, promoting wound healing, and supporting lymphatic circulation^{17,25}. The smaller size of HA35 allows it to penetrate the skin more effectively and work at a deeper, more cellular level compared to traditional HA. This enhanced permeability means that HA35 can provide both immediate cosmetic benefits, such as improved hydration and reduced skin roughness, as well as address underlying inflammatory conditions. As our study showed, the treatment was effective within the first 20 minutes, making it an ideal candidate for quick recovery or enhancement of skin quality, with significant improvements observed within the 24-hour mark. These results underscore the potential of HA35 as a versatile treatment option for both cosmetic concerns, such as dull complexion and rough texture, and more serious inflammatory symptoms, including erythema and skin thickening.

The microneedling technique, particularly when combined with negative pressure, has become increasingly popular due to its ability to promote the transdermal delivery of bioactive substances⁹⁻¹³. The creation of microchannels in the skin allows for deeper penetration of hyaluronic acid and other active ingredients, which enhances treatment efficacy for hard-to-reach tissues²⁶. In our study, negative pressure microneedling further amplified the effectiveness of HA35 by allowing it to permeate the skin more efficiently than standard methods. This technique also helps to minimize localized inflammation, which can be a common side effect of traditional injection techniques. The negative pressure generated by the microneedling device creates an optimal environment for HA35 to be absorbed by deeper layers of the skin, reducing the need for more invasive procedures. The rapid onset of improvements in skin hydration and appearance after treatment further supports the hypothesis that negative pressure microneedling enhances the bioavailability of HA35. This mechanism of action is in line with findings by Wu et al., who demonstrated that hyaluronic acid delivered via microneedling showed greater skin permeation compared to traditional injection methods²⁷. Additionally, the absence of significant pain or persistent swelling following the procedure, as reported by participants in this study, suggests that HA35 may be better tolerated than high molecular weight HA or collagen injections. This is an important consideration for patients who are sensitive to post-treatment discomfort or those who experience prolonged side effects with traditional dermal fillers²⁸.

One of the most promising aspects of HA35 is its potential for anti-inflammatory treatments beyond purely cosmetic applications. As highlighted in previous studies, low molecular weight hyaluronan fragments

have been shown to bind to receptors such as CD44 and TLR2, which play key roles in regulating inflammation and wound healing^{29,30}. These findings are supported by our results, where the treatment demonstrated a significant reduction in erythema, skin thickness, and hardness within just one hour of application. The ability of HA35 to reduce inflammatory markers so quickly may make it a valuable treatment for conditions like rosacea, acne, and other inflammatory skin disorders, where inflammation is a major contributor to skin damage and discomfort^{15,17}. Furthermore, the sustained effect observed at the four-week follow-up suggests that HA35 not only improves the immediate appearance and feel of the skin but also promotes longer-term healing and tissue recovery. This is an important consideration for patients seeking non-invasive treatments with lasting effects, as the results were still visible and clinically relevant a month after a single injection. These prolonged effects are consistent with the findings of Treger et al., who reported that repeated injections of low molecular weight hyaluronan improved chronic wound healing over extended periods¹⁸.

Despite its promising findings, this study has several limitations inherent to its proof-of-concept design. The absence of a control group limits our ability to isolate the specific effects of HA35 from other potential confounding factors, and the lack of a placebo group prevents us from fully ruling out the placebo effect. Additionally, the small sample size (n=16), while sufficient for an exploratory study, reduces the statistical power and generalizability of the findings. A larger, stratified study would be necessary to confirm the observed effects and further investigate potential differences in treatment response based on age and sex. The study's four-week follow-up period allowed for an assessment of short-term effects but was insufficient to determine the long-term durability of the treatment. Given that skin regeneration occurs over multiple cycles, future research should extend follow-up durations (e.g., 3-6 months) to assess the persistence of benefits and the potential cumulative effects of repeated treatments. Moreover, while the study demonstrated improvements in hydration, brightness, and inflammation, response variability among different patient populations remains an open question. Individuals with severe chronic skin conditions, impaired barrier function, or extensive fibrosis may experience different outcomes, highlighting the need for further research to identify the subpopulations that would benefit most from this intervention.

Despite these limitations, HA35 may have broader dermatological applications beyond cosmetic and inflammatory skin concerns. Its potential role in scar treatment, skin aging, and post-surgical recovery warrants further exploration. Future research should focus on refining treatment protocols, evaluating long-

term efficacy, and conducting comparative studies with existing therapeutic options to establish HA35 as a viable alternative in both aesthetic and medical dermatology. Understanding how different patient profiles respond to HA35-based therapies will be critical in optimizing its clinical applications and ensuring its effectiveness across diverse skin conditions.

Conclusion

In conclusion, the combination of HA35 with a negative pressure microneedling delivery system offers a safe, effective, and non-pharmaceutical alternative for treating both cosmetic skin issues and chronic inflammatory conditions. This study demonstrates significant improvements in hydration, brightness, and inflammation with minimal side effects. While the results are promising, future controlled trials with larger sample sizes and extended follow-up periods are necessary to validate these findings and explore the long-term therapeutic potential of HA35. The high patient satisfaction and sustained improvements observed in this study indicate that HA35 represents a valuable addition to the growing field of aesthetic dermatology.

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Disclosure

All potential conflicts of interest, including industry support, were disclosed in accordance with ethical guidelines. The study was conducted independently, and any industry involvement, such as equipment provision or research funding, was transparently stated.

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