

Overnight Occlusive Topical Application of High-Concentration 35 kDa Hyaluronic Acid Fragments for Facial Erythema and Subcutaneous Fat: A Case Series.

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Abstract

Background: The naked mole rat (NMR) exhibits an exceptionally high concentration of hyaluronan (HA) in the skin and subcutaneous tissues, minimal subcutaneous fat accumulation, and a low incidence of inflammatory skin conditions. These features suggest a potential role for high-concentration HA in regulating cutaneous inflammation and adipose-related facial appearance.

Methods: This exploratory case series included five adults seeking non-invasive improvement of facial erythema and localized subcutaneous fat. A 10% formulation of 35 kDa HA fragments was applied to the entire face under occlusive conditions overnight once every two days for a total of five applications. Facial subcutaneous fat appearance, inflammatory erythema, skin radiance, and nasal alar pore condition were assessed at baseline, after the first application, and after the fifth application using a standardized 0–10 numerical rating scale (NRS).

Results: All participants demonstrated consistent reductions in facial subcutaneous fat appearance and inflammatory erythema, with visible improvement observed after the first overnight application and further enhancement following repeated treatment. Skin radiance improved and nasal alar pore enlargement was attenuated in all cases. No local or systemic adverse events were reported.

Conclusions: Overnight occlusive topical application of high-concentration 35 kDa HA fragments was well tolerated and associated with rapid improvements in facial erythema, subcutaneous fat appearance, skin radiance, and pore condition. These preliminary findings support further investigation of low-molecular-weight HA fragments as a non-invasive approach for facial aesthetic improvement in controlled clinical studies.

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2 **Introduction:-**

3 The NMR has attracted substantial scientific interest due to its extraordinary longevity and remarkably low
4 incidence of inflammation and neoplastic disease. A defining biological characteristic of this species is the
5 exceptionally high concentration of HA in its skin and subcutaneous tissues, accounting for approximately 6% of
6 tissue composition, which is markedly higher than that observed in humans and other mammals. Notably, naked
7 mole rats exhibit minimal subcutaneous fat accumulation and rarely develop inflammatory skin disorders [1,2].
8 These features suggest that high levels of HA may play an important role in maintaining adipose homeostasis and
9 suppressing cutaneous inflammation.

10 Increasing evidence indicates that the biological activity of HA is highly dependent on its molecular weight. In
11 contrast to high-molecular-weight HA, HA fragments within specific molecular weight ranges have been shown to
12 modulate adipocyte differentiation, inflammatory signaling, and neuro-sensory pathways through receptor-mediated
13 mechanisms [3,4]. Our research group previously demonstrated that continuous oral administration of high-dose,
14 intestinally permeable 70 kDa HA fragments led to reductions in facial subcutaneous fat appearance, attenuation of
15 inflammatory erythema, and improvement in overall facial condition within 20–40 days (Chinese Patent Application
16 No. 202411344317).

17 More recently, we observed that topical application of a 10% high-concentration 35 kDa HA fragment
18 formulation produced rapid relief of cutaneous pruritus and superficial pain [5]. Pharmacokinetic analyses suggested
19 that this molecule does not readily penetrate into the dermis or subcutaneous tissue within short time frames,
20 implying that its biological effects may not depend on conventional transdermal absorption. Building upon these
21 observations, the present study aimed to explore the effects of repeated overnight occlusive topical application of a
22 10% high-concentration 35 kDa HA fragment formulation on facial subcutaneous fat appearance, inflammatory
23 erythema, skin radiance, and nasal alar pore condition.

24 **Cases and Methods**

25 **PARTICIPANTS**

26 This case series included five Asian participants (three females and two males) who presented to the Department of
27 Aesthetic Medicine at Changchun Jiahe Plastic Surgery Hospital, China. All participants sought non-invasive
28 improvement of facial appearance due to localized subcutaneous fat accumulation and/or facial erythema.

29 Participants ranged in age from 27 to 68 years. Participant 1 was a 27-year-old female with a normal body mass
30 index (BMI), a history of chronic sleep deprivation, and mildly sensitive skin. Her primary concerns included mild
31 subcutaneous fat accumulation in the cheek and nasal alar regions accompanied by recurrent facial flushing, with no
32 history of systemic dermatologic disease. Participant 2 was a 28-year-old male with a slightly elevated BMI,
33 presenting with fat accumulation along the cheeks and mandibular border, as well as pronounced nasal alar pore
34 enlargement. No active inflammatory skin conditions were reported. Participant 3 was a 42-year-old premenopausal
35 female with increased subcutaneous fat in the cheeks and mandibular regions, accompanied by dull erythema in the
36 central facial area and occasional acneiform lesions. Participant 4 was a 56-year-old postmenopausal female
37 exhibiting facial skin laxity, reduced skin radiance, prominent subcutaneous fat accumulation in the temporal and
38 cheek regions, and enlarged nasal alar pores. Participant 5 was a 68-year-old male with evident age-related skin
39 changes, uneven facial fat distribution, and chronic erythema with enlarged pores in the nasal alar region.

40 All participants demonstrated full decision-making capacity and were able to understand and independently use a
41 standardized 0–10 NRS[6,7] to complete self-assessments and report outcome measures. None of the participants
42 had received fat-reduction treatments, medical aesthetic injections, or professional facial care within two weeks
43 prior to enrollment.

44 **INTERVENTION**

45 All participants underwent an identical intervention protocol. Each evening before sleep, a 10% high-concentration
46 35 kDa HA fragment formulation (product code: Q/0285HND045) was evenly applied to the entire face. The treated
47 area was then covered with plastic wrap or a protective occlusive film to prevent premature drying, and the
48 formulation was left in place overnight. Facial cleansing was performed the following morning.

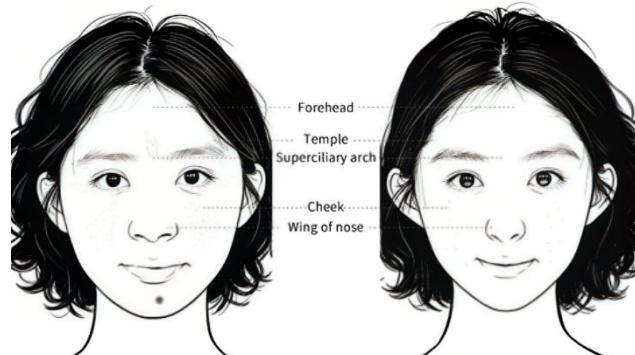
51 The intervention was administered once every two days, with a total of five applications completed over a 10-day
52 period.

53 **OUTCOME ASSESSMENT**

54 A standardized 0–10 numerical rating scale (6,7) was used to quantitatively evaluate facial changes at baseline, after
55 one application, and after completion of five applications. The assessed parameters included facial subcutaneous fat
56 thickness, dark inflammatory erythema, skin radiance, and nasal alar pore enlargement.

57 Based on the schematic illustration shown in Figure 1, visual inspection combined with tactile palpation was used to
58 assess the distribution and relative thickness of subcutaneous fat in the forehead, brow ridge, temples, cheeks, and
59 nasal alar regions. Visual inspection was also employed to evaluate the extent of dark inflammatory erythema in
60 these regions and to assess changes in nasal alar pore appearance.

61 Scoring criteria were defined as follows. For facial subcutaneous fat thickness, a score of 0 indicated normal
62 thickness, while 10 represented the theoretical maximum thickness. For dark inflammatory erythema in the cheek
63 and nasal alar regions, 0 indicated absence of erythema and 10 represented the theoretical maximum severity. For
64 facial skin radiance, 0 indicated normal radiance and 10 represented the poorest theoretical radiance. For nasal alar
65 pore enlargement, 0 indicated normal pores without enlargement and 10 represented the most severe theoretical
66 enlargement.



67
68 Figure 1. Schematic illustration of visual assessment of facial parameters before and after treatment. Figure 1A
69 represents the estimated facial condition at baseline, and Figure 1B represents the estimated condition after five
70 applications.

71 **RESULTS**

72 After five overnight occlusive topical applications, all participants exhibited a sustained decreasing trend in
73 subcutaneous fat thickness across multiple facial anatomical regions. The most pronounced improvements were
74 observed in the forehead, brow ridge, cheeks, and nasal alar regions, as summarized in Table 1. The severity of dark
75 inflammatory erythema in the cheek and nasal alar regions decreased concurrently, and in most participants, visually
76 perceptible improvement was already evident after the first application.

77 Facial skin radiance scores demonstrated a progressive decline in the forehead, brow ridge, and central facial
78 regions, indicating improvement in skin dullness and overall luminosity. The degree of nasal alar pore enlargement
79 also decreased with increasing numbers of applications. Throughout the study period, no participant reported local
80 irritation, burning sensation, desquamation, or delayed adverse reactions, and no systemic adverse events were
81 observed, suggesting good tolerability of the occlusive topical regimen.

82 Table 1. Quantitative scores (0–10) of facial parameters before and after treatment

Evaluation Parameter	Assessment Site	Baseline	After 1 treatment	After 5 treatments
Facial subcutaneous fat thickness	Forehead	3.6 ± 1.4	2.6 ± 1.4*	0.8 ± 0.7**
	Brow ridge	4.0 ± 1.8	3.0 ± 1.8*	1.0 ± 0.9**
	Temple	2.2 ± 1.0	2.2 ± 1.0 ns	0.2 ± 0.4**
	Cheek	4.2 ± 1.8	3.2 ± 1.8*	1.0 ± 0.9**
	Nasal alar	3.0 ± 0.9	2.4 ± 0.5*	0.8 ± 0.4**
Dark inflammatory erythema	Cheek	3.2 ± 1.2	2.2 ± 1.2*	0.2 ± 0.4**
	Nasal alar	2.6 ± 0.8	1.8 ± 0.7*	0.4 ± 0.5**
Facial skin radiance	Forehead and brow ridge	3.0 ± 0.9	2.0 ± 0.9*	0.2 ± 0.4**
	Temple and cheek	3.6 ± 0.5	2.6 ± 0.5*	0.4 ± 0.5**
	Nasal alar and facial region	4.0 ± 0.9	3.0 ± 0.9*	0.8 ± 0.7***
Pore enlargement	Nasal alar	3.0 ± 0.6	2.4 ± 0.5*	0.6 ± 0.5**

*Data are presented as mean ± SD. Statistical significance is based on comparisons with baseline: ns, P > 0.05; *P < 0.05; **P < 0.01; ***P < 0.001.

Figure 2 presents representative clinical images from two participants before treatment and after five applications. Visible improvements were observed in nasal alar pore enlargement, facial dark erythema, skin radiance, and nasal alar subcutaneous fat appearance.



Figure 2. Representative facial images before and after treatment.

Discussion

This exploratory case series suggests that five overnight occlusive topical applications of a 10% high-concentration 35 kDa HA fragment formulation were associated with stable and consistent aesthetic improvements across multiple facial parameters. Improvements were observed in all assessed domains, including the appearance of subcutaneous

93 fat thickness, inflammatory erythema, skin radiance, and nasal alar pore appearance, as summarized in Table 1 and
94 illustrated in Figure 2. Collectively, these findings align with the inflammation-resistant phenotype associated with
95 high tissue hyaluronan content in naked mole rats and are consistent with observations reported in our previous
96 clinical and experimental studies [1–5]. Together, they provide preliminary clinical-level support for the potential
97 role of high-concentration, molecular-weight-specific HA fragments in facial aesthetic modulation and
98 inflammatory regulation.

99 Notably, partial improvements were already apparent following the first overnight occlusive application, indicating
100 that the observed effects may not depend exclusively on long-term structural tissue remodeling. Instead, relatively
101 rapid regulatory processes—potentially involving neuro-inflammatory signaling, microcirculatory modulation, or
102 changes in tissue hydration dynamics—may contribute to the early clinical responses. Previous studies have
103 suggested that 35 kDa HA fragments can interact with transient receptor potential ion channels in peripheral sensory
104 nerve endings and influence downstream inflammatory signaling pathways, thereby reducing local inflammatory
105 sensitivity and indirectly affecting cutaneous blood flow, tissue tension, and adipose homeostasis [5]. Although the
106 present study did not directly investigate these mechanisms, the rapid onset of visible changes observed under
107 occlusive conditions is compatible with such regulatory pathways.

108 From a clinical perspective, facial erythema, localized subcutaneous fat accumulation, and pore enlargement are
109 often managed as independent aesthetic concerns. However, emerging evidence indicates that these features are
110 frequently interconnected and associated with chronic low-grade cutaneous inflammation, microvascular dilation,
111 and dysregulated adipose metabolism. In this context, the observed simultaneous improvement across multiple facial
112 parameters suggests a shared underlying regulatory effect rather than isolated cosmetic changes.

113 Compared with topical corticosteroids, which are commonly used to suppress facial inflammation but are limited by
114 risks such as skin atrophy, barrier impairment, and rebound erythema, the 35 kDa HA fragment formulation applied
115 in this study demonstrated a relatively rapid improvement profile without observable local or systemic adverse
116 effects [8–10]. This favorable tolerability profile may offer potential advantages for repeated or longer-term use,
117 particularly in individuals with inflammation-prone facial skin.

118 Several limitations of this study should be acknowledged. The sample size was small, and outcome assessments
119 were based primarily on subjective NRSs, without objective imaging, biochemical markers, or histological
120 validation. In addition, the use of occlusive application may have amplified local microenvironmental effects, and
121 the efficacy and durability of this formulation under routine, non-occlusive topical conditions remain to be
122 determined. Future studies incorporating larger cohorts, controlled study designs, and objective assessment tools—
123 such as high-frequency skin ultrasound or optical imaging—are warranted to confirm these findings and further
124 clarify the underlying biological mechanisms.

125 Conclusion

126 Overnight occlusive topical application of a 10% high-concentration 35 kDa HA fragment formulation was
127 associated with visible reductions in the appearance of facial subcutaneous fat and inflammatory erythema,
128 improvement in nasal alar pore appearance, and enhancement of overall skin radiance. The intervention
129 demonstrated a rapid onset of effect and good tolerability in this small case series. Although preliminary in nature,
130 these findings suggest that high-concentration, low-molecular-weight HA fragments may represent a safe, non-
131 invasive, and potentially effective approach for facial aesthetic improvement and skin condition modulation,
132 meriting further investigation in larger, well-controlled clinical studies.

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