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ORIGINAL RESEARCH

Safety and Efficacy of Hyaluronic Acid-Based Filler for Neck Wrinkles: A Prospective, Multicenter, Randomized, Parallel-Controlled Non-Inferiority Trial

Meng Jiang[1], Haiyan Cheng[1], Yan Li[1], Hongmei Ai[2], Jun Li[3], Yanjun Liang[4], Wei Xu[1]

[1]Department of Dermatology and Venereology, Beijing Friendship Hospital, Capital Medical University, Beijing, People's Republic of China; [2]Department of Plastic Surgery, Emergency General Hospital, Beijing, People's Republic of China; [3]Department of Medical Cosmetology, Nanjing Women and Children's Healthcare Hospital, Nanjing, People's Republic of China; [4]Department of Medical Cosmetology, Taiyuan Central Hospital, Taiyuan, People's Republic of China

Correspondence: Wei Xu, Department of Dermatology and Venereology, Beijing Friendship Hospital, Capital Medical University, No. 95 Yong'an Road, Xicheng District, Beijing, 100050, People's Republic of China, Email 2403649155@qq.com

Background: Horizontal neck lines are an early and conspicuous marker of cutaneous aging. Intradermal hyaluronic acid (HA) injections have become a standard minimally invasive countermeasure, yet comparative data for composite HA solutions in Asian populations remain scarce.

Purpose: To evaluate the efficacy and safety of injectable sodium hyaluronate composite solution (NCTF® 135 HA) compared with injectable sodium hyaluronate composite solution (HEARTY®) for the correction of moderate-to-severe neck wrinkles.

Methods: In this prospective, multicenter, randomized, evaluator-blinded, active-controlled, non-inferiority trial, 188 subjects with moderate-to-severe neck wrinkles were randomly assigned (1:1) to the experimental group or the control group, with both groups receiving three sessions of non-cross-linked injectable sodium hyaluronate composite solution at 4-week intervals. Improvement of Allergan Transverse Neck Lines Scale (ATNLS), subject-assessed Global Aesthetic Improvement Scale (GAIS) and adverse events (AEs) were evaluated and compared before the 3 injection sessions and at 4, 12, and 24 weeks post-final injection.

Results: At week 4 post-final injection, the ATNLS response rates were 88.30% in the experimental group and 85.11% in the control group, respectively, with a between-group difference of 3.19% (95% confidence interval (CI): [−0.0723, 0.0987], $p = 0.5410$), demonstrating non-inferiority of the experimental treatment to the active control. Among the secondary endpoints, neither ATNLS response rates at additional time points nor subject-assessed GAIS responder rates showed statistically significant differences between groups. A total of 128 adverse events were reported, with no statistically significant difference between groups: 26 (27.66%) in the experimental group and 38 (40.43%) in the control group. No device- or procedure-related serious adverse events occurred.

Conclusion: Injectable sodium hyaluronate composite solution (non-cross-linked) provides safe, effective, and non-inferior correction of moderate-to-severe neck wrinkles compared with active control, expanding minimally invasive therapeutic options for cervical rejuvenation.

Keywords: multicenter, neck wrinkles, hyaluronic acid, mesotherapy, neck rejuvenation

Introduction

Neck aging is characterized by skin laxity, atrophy, loss of elasticity, platysmal banding, fat redistribution, and prominent horizontal necklines, which frequently make the neck appear significantly older than the face and serve as the most conspicuous and difficult-to-conceal hallmark of cervical aging.[1,2] Objective biophysical studies reveal a progressive decline in neck skin elasticity with aging, dropping from approximately 75% in young adults to 56% in individuals over 50. Concurrently, skin roughness and transepidermal water loss increase in correlation with the severity of horizontal neck folds.[3] While population-based epidemiological data remain limited, clinical observations indicate that visible neck

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lines are already prevalent from the third decade of life and become nearly universal after the fourth decade.[4,5] Notably, their onset is increasingly observed in younger individuals, likely accelerated by sustained forward-head posture associated with prolonged use of smartphones and computers. Beyond biophysical changes, neck aging is often perceived as more age-revealing than facial aging. This perception can lead to significant psychosocial impacts, including increased self-consciousness, avoidance of revealing clothing, and diminished self-esteem, thereby highlighting the clinical and aesthetic significance of effective therapeutic solutions.[6]

Although various rejuvenation modalities, including energy-based devices, surgical neck lifts, and botulinum toxin injections, have been employed, their application to the neck region remains challenging due to thin skin, high mobility, risk of complications, prolonged downtime, and often suboptimal or transient outcome.[7–10] Consequently, there remains a significant unmet clinical need for safe, effective, and minimally invasive treatments specifically targeting horizontal necklines. Hyaluronic acid (HA)-based injectable fillers have emerged as one of the most promising solutions owing to their excellent biocompatibility, immediate volumizing effect, and ability to improve skin hydration and elasticity.[11,12] Among these, the experimental product is a unique HA-based composite solution combining non-crosslinked hyaluronic acid with 60 active ingredients, designed to exert both filling and intense biorevitalizing effects.[13,14] Although previous studies have confirmed its efficacy and safety in improving facial skin quality and superficial wrinkles, high-level evidence regarding its specific performance in correcting horizontal necklines, particularly in Asian populations, is still limited. The control product, a well-established HA filler, is currently one of the most frequently used and clinically validated products for neck wrinkles in China.[15] However, it remains unclear whether the experimental treatment is non-inferior to the control in reducing neck wrinkles while potentially providing additional benefits in skin hydration, texture, injection comfort, and recovery due to its unique non-crosslinked and biorevitalizing formulation.

Therefore, this prospective, multicenter, randomized, parallel-controlled, non-inferiority trial was conducted to evaluate the efficacy and safety of the experimental product compared with the active control for the treatment of moderate to severe horizontal necklines in Chinese subjects.

Materials and Methods

Study Design

This was a prospective, multicenter, randomized, active-controlled, non-inferiority trial conducted from March 2021 to December 2021. Four tertiary institutions participated: Beijing Friendship Hospital, Emergency General Hospital, Nanjing Women and Children's Healthcare Hospital, and Taiyuan Central Hospital. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Beijing Friendship Hospital, Capital Medical University (No. 2020-P1-Device-012-02), and subsequently ratified by the ethics committees of the other three participating research centers. The trial was registered with the Chinese Clinical Trial Registry (ChiCTR2100045588). All participants provided written informed consent prior to enrollment.

Participants

A total of 188 healthy participants aged 18–70 years, with moderate to severe neck wrinkles (severity score of 2 or 3 according to the ATNLS Wrinkle Assessment[16]), were recruited. Patients with a history of severe allergic reactions, known hypersensitivity to hyaluronic acid-based products or to any component of the formulation, known history of keloid formation, any previous cosmetic procedures in the neck area within 24 weeks before enrolment, history of radiotherapy to the head and neck region within the past year, obvious scars, active skin diseases, cancerous/precancerous lesions, or unhealed wounds in the neck area, current or recent ($\leq$ 2 weeks) use of anticoagulant or antiplatelet drugs, or known coagulopathy, history of severe diseases or significant dysfunction of major organs, or a history of immune dysfunction, pregnancy, lactation, or intention to become pregnant during the study were excluded from the study.

Interventions

Both the experimental product (NCTF® 135 HA, 3mL/vial, Laboratoires FILL-MED, France) and the control product (HEARTY®, 2.5mL/syringe, Beijing IMEIK Technology Development Co., Ltd, China) were injectable sodium hyaluronate-based composite solutions, characterized by a composition of non-cross-linked sodium hyaluronate and multiple anti-aging nutrients. All enrolled subjects were randomized in a 1:1 ratio to receive either the experimental product or the control product with proven efficacy in improving neck wrinkles, as an active control, and were blinded to treatment allocation throughout the study. A central interactive web response system (IWRS) was used for randomization in this clinical trial.

To minimize discomfort during the procedure, subjects received local anesthesia with 10g compound lidocaine cream (25 mg prilocaine + 25 mg lidocaine per gram) on the horizontal neck lines. Then they were placed in a supine position for optimal exposure of the neck wrinkles, followed by standard antisepsis with povidone-iodine. The product was administered utilizing a retrograde linear threading technique along the neck folds with a 30G × 4 mm needle inserted at a 10°- 15°angle. The needle was advanced parallel to the skin surface until its full length was within the dermis. Upon confirmation that aspiration was negative for blood reflux, slow injection of the filler was initiated concurrent with needle withdrawal. Each individual injection administered approximately 0.05 to 0.1mL of the filler, with a maximum single-session dose of 3 mL for the entire neck wrinkles. The immediate outcome of the injection was the disappearance of neck folds, with a discernible strip-shaped prominence in the dermal layer. A local cold compress was applied post-injection to prevent edema and bruising. Each subject received three injection sessions administered at intervals of 4 weeks (± 7 days).

Efficacy Outcomes

Efficacy assessments were performed based on standardized neck photographs of each subject using ATNLS assessed by an independent evaluator and GAIS score was assessed by the subjects. A standardized photographic protocol was established to ensure reproducibility and comparability of images across all visits. Photographs of the anterior and bilateral lateral neck were captured at each visit using a digital camera (Canon EOS R6, Canon Inc., Tokyo, Japan) equipped with a Canon RF 24–105mm f/4L IS USM lens, set at a focal length of 50mm to minimize distortion. Camera settings were standardized as follows: aperture f/8.0, shutter speed 1/125s, ISO 400, and white balance set to 5600K. The primary efficacy outcome was the non-inferiority test of the improvement rate in the ATNLS between the experimental and control groups, assessed by an independent evaluator at week 4 post-final injection compared to baseline. An improvement was considered effective if the subject exhibited a decrease of 1 point or more in the ATNLS score post-injection compared to baseline.

Secondary outcomes were (i) changes in ATNLS scores and the response rate in the ATNLS assessed by an independent evaluator at other scheduled visits; (ii) improvement rate in subject-assessed GAIS scores at the following time points: prior to the second injection, prior to the third injection, and at weeks 4, 12, and 24 after the final treatment compared to baseline. The GAIS improvement score was defined as follows: 1 = very much improved, 2 = much improved, 3 = improved, 4 = no change, and 5 = worse.

Safety Outcomes

At each follow-up visit, subjects were queried regarding procedure-related adverse events (AEs), such as injection-site bruising, pain, edema or redness. Events were recorded for severity, duration, and relationship to treatment. Laboratory tests were performed at baseline (pre-injection) and at weeks 4 and 12 post-final injection for all subject, including blood biochemistry, complete blood count, urinalysis and pregnancy test (for women of childbearing potential only). Serious AEs and device- or procedure-related AEs were tracked throughout the study.

Sample Size Calculation

The sample size was calculated for a controlled, non-inferiority design with 1:1 allocation. It was calculated based on the primary endpoint of ATNLS improvement rate. With an expected rate of 95% in both groups, a non-inferiority margin of

−10%, a one-sided alpha (α) of 0.025, and 80% power (β = 0.2), the required sample size was determined using the formula for two proportional groups. The calculation yielded 75 participants per group. Accounting for a potential dropout rate of 20% and design effects from block randomization, the final planned enrollment was set at 188 participants.

Statistical Analysis

The statistical analysis was conducted utilizing SAS 9.4. The baseline observation carried forward (BOCF) imputation was implemented for missing data in the primary variable. The primary efficacy endpoint was assessed using a non-inferiority analysis. Continuous data are presented as mean ± standard deviation ($x \pm s$) and categorical data are summarized as frequency counts and percentages (%). Statistical significance was calculated by a Student's Test for paired series or the Wilcoxon Test. Categorical variables were compared using the Chi-square test (χ^2) or Fisher's exact test. A one-sided lower 95% confidence interval (CI) was used in analysis of the primary endpoint, with a non-inferiority margin of –10% absolute difference. A p-value < 0.05 was considered statistically significant for secondary endpoints and safety profiles.

Results

Baseline Characteristics

A total of 188 enrolled subjects were randomized and received treatment (94 in the experimental group and 94 in the control group). Ultimately, 180 subjects (91 in the experimental group and 89 in the control group) were included in the primary endpoint analysis. As shown in Table 1, mean age was virtually identical between the two groups (39.12 ± 9.24 years vs 38.82 ± 10.08 years; $p = 0.68$), and the sex distribution was likewise comparable (97.87% vs 95.74% female; $p = 0.41$). All subjects were Asian and the proportion of Han ethnicity exceeded 96% in both groups ($p = 0.66$). Mean injected volumes across the three sessions were virtually identical between groups (all $p > 0.05$). There were no statistically significant differences in age, gender, race or injection doses between the groups.

Table 1 Baseline Demographic and Injection Data

Characteristic	Experimental Group (N = 94)	Control Group (N = 94)	P Value
Age (years)			0.6805
Mean ± SD	39.12 ± 9.24	38.82 ± 10.08	
Median (range)	39 (23–62)	37 (23–64)	
Sex, N (%)			0.4066
Male	2 (2.13%)	4 (4.26%)	
Female	92 (97.87%)	90 (95.74%)	
Race, N (%)			0.6617
Han	91 (96.81%)	92 (97.87%)	
Mongolian	1 (1.06%)	0 (0%)	
Man	2 (2.13%)	2 (2.13%)	
First injection dose (mL)			0.6858
Mean ± SD	2 ± 0.02	1.99 ± 0.03	
Median (range)	2 (1.9–2.0)	2 (1.8–2.0)	
Second injection dose (mL)			0.0751
Mean ± SD	1.97 ± 0.06	1.98 ± 0.05	
Median (range)	2 (1.7–2.0)	2 (1.75–2.0)	
Third injection dose (mL)			0.0822
N	92	94	
Mean± SD	1.98 ± 0.05	1.99 ± 0.03	
Median (range)	2 (1.8–2.0)	2 (1.9–2.0)	

Abbreviation: SD, standard deviation.

Primary Efficacy Outcome

Baseline ATNLS scores were equivalent (experimental 2.59 ± 0.50 vs control 2.57 ± 0.50). Four weeks after the final injection, mean scores had fallen to 1.65 ± 0.57 and 1.70 ± 0.55, respectively. Based on this definition, where a reduction of ≥1 point in the ATNLS score from baseline was considered an effective response (improvement), the response rates at week 4 post-final injection were 88.30% in the experimental group and 85.11% in the control group, respectively (Table 2 and Figure 1). Difference in response rates was 3.19% (95% CI: [−0.0723, 0.0987]). Since the lower limit of the 95% confidence interval exceeded the non-inferiority margin of −10%, experimental product was formally non-inferior to the

Table 2 Changes in ATNLS Scores and Response Rates Assessed by an Independent Evaluator at Different Follow-Up Time Points

Changes in ATNLS Scores	Experimental Group	Control Group	P Value
Baseline			
N (missing)	94 (0)	94 (0)	
Mean ± SD	2.59 ± 0.50	2.57 ± 0.50	0.8841
Median (range)	3 (2–3)	3 (2–3)	
Grade 2	39 (41.49%)	40 (42.55%)	
Grade 3	55 (58.51%)	54 (57.45%)	
Pre-dose 2			
N (missing)	94 (0)	94 (0)	
Mean ± SD	2.40 ± 0.61	2.44 ± 0.61	0.6924
Median (range)	2 (1–3)	2.5 (1–3)	
Grade 1	6 (6.38%)	6 (6.38%)	
Grade 2	44 (46.81%)	41 (43.62%)	
Grade 3	44 (46.81%)	47 (50%)	
Response rate	16 (17.02%)	13 (13.83%)	0.5472
Pre-dose 3			
N (missing)	94 (0)	92 (2)	
Mean ± SD	2.14 ± 0.7	2.21 ± 0.64	0.5376
Median (range)	2 (1–3)	2 (1–3)	
Grade 1	17 (18.09%)	11 (11.96%)	
Grade 2	47 (50%)	51 (55.43%)	
Grade 3	30 (31.91%)	30 (32.61%)	
Response rate	41 (43.62%)	34 (36.17%)	0.2992
Week 4 post-final injection			
N (missing)	91 (3)	89 (5)	
Mean ± SD	1.65 ± 0.57	1.70 ± 0.55	0.5410
Median (range)	2 (1–3)	2 (1–3)	
Grade 1	36 (39.56%)	31 (34.83%)	
Grade 2	51 (56.04%)	54 (60.67%)	
Grade 3	4 (4.40%)	4 (4.49%)	
Response rate	83 (88.30%)	80 (85.11%)	0.5219
Week 12 post-final injection			
N (missing)	90 (4)	90 (4)	
Mean ± SD	1.94 ± 0.64	1.94 ± 0.68	0.9885
Median (range)	2 (1–3)	2 (1–3)	
Grade 1	21 (23.33%)	23 (25.56%)	
Grade 2	53 (58.89%)	49 (54.44%)	
Grade 3	16 (17.78%)	18 (20%)	
Response rate	56 (59.57%)	57 (60.64%)	0.8832

(*Continued*)

Table 2 (Continued).

Changes in ATNLS Scores	Experimental Group	Control Group	P Value
Week 24 post-final injection			
N (missing)	87 (7)	89 (5)	
Mean ± SD	2.43 ± 0.60	2.38 ± 0.65	0.7309
Median (range)	2 (1–3)	2 (1–3)	
Grade 1	5 (5.75%)	8 (8.99%)	
Grade 2	40 (45.98%)	39 (43.82%)	
Grade 3	42 (48.28%)	42 (47.19%)	
Response rate	12 (12.77%)	19 (20.21%)	0.1707

active comparator for improving moderate-to-severe horizontal neck lines. Representative subject photographs are presented in Figures 2 and 3.

Secondary Efficacy Outcomes

The mean ATNLS scores, score changes and response rates for both groups at other scheduled visits are presented in Table 2. The mean ATNLS scores in the experimental group were 2.40 ± 0.61, 2.14 ± 0.7, 1.94 ± 0.64, and 2.43 ± 0.60, while those in the control group were 2.44 ± 0.61, 2.21 ± 0.64, 1.94 ± 0.68, and 2.38 ± 0.65, assessed at pre-dose 2, pre-dose 3, and at weeks 12 and 24 post-final treatment, respectively (Table 2). Response rates similarly demonstrated dynamic profiles, with experimental group rates of 17.02%, 43.62%, 59.57%, 12.77% and control group rates of 13.83%, 36.17%, 60.64%, 20.21% (Figure 1). As a result, no statistically significant difference were observed in either the ATNLS scores or the treatment response rates between the two groups (all $p > 0.05$). GAIS improvement rates, as

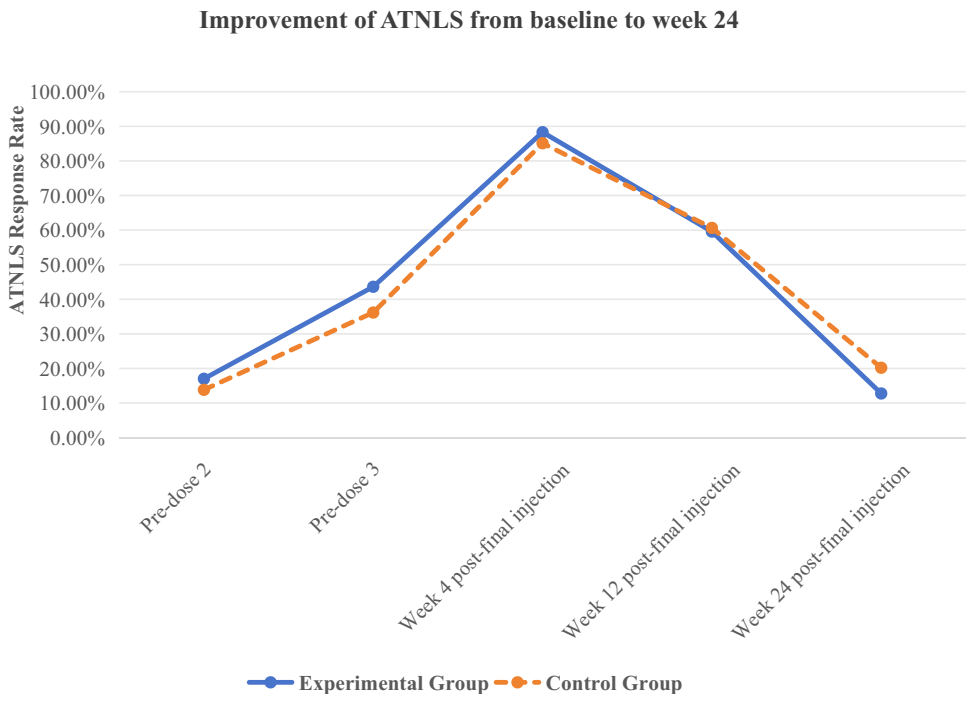

Figure 1 ATNLS response rates (≥ 1 point reduction from baseline) assessed by blinded independent evaluator over the 24-week study period. The ATNLS response rates at each time point were as follows. Pre-dose 2: 17.02% (experimental group) and 13.83% (control group); Pre-dose 3: 43.62% and 36.17%; Week 4 post-final injection: 88.30% and 85.11%; Week 12 post-final injection: 60.64% and 59.57%; Week 24 post-final injection: 12.77% and 20.21%, respectively. Peak responses in both groups were observed at week 4 post-final injection. No significant between-group differences were detected.

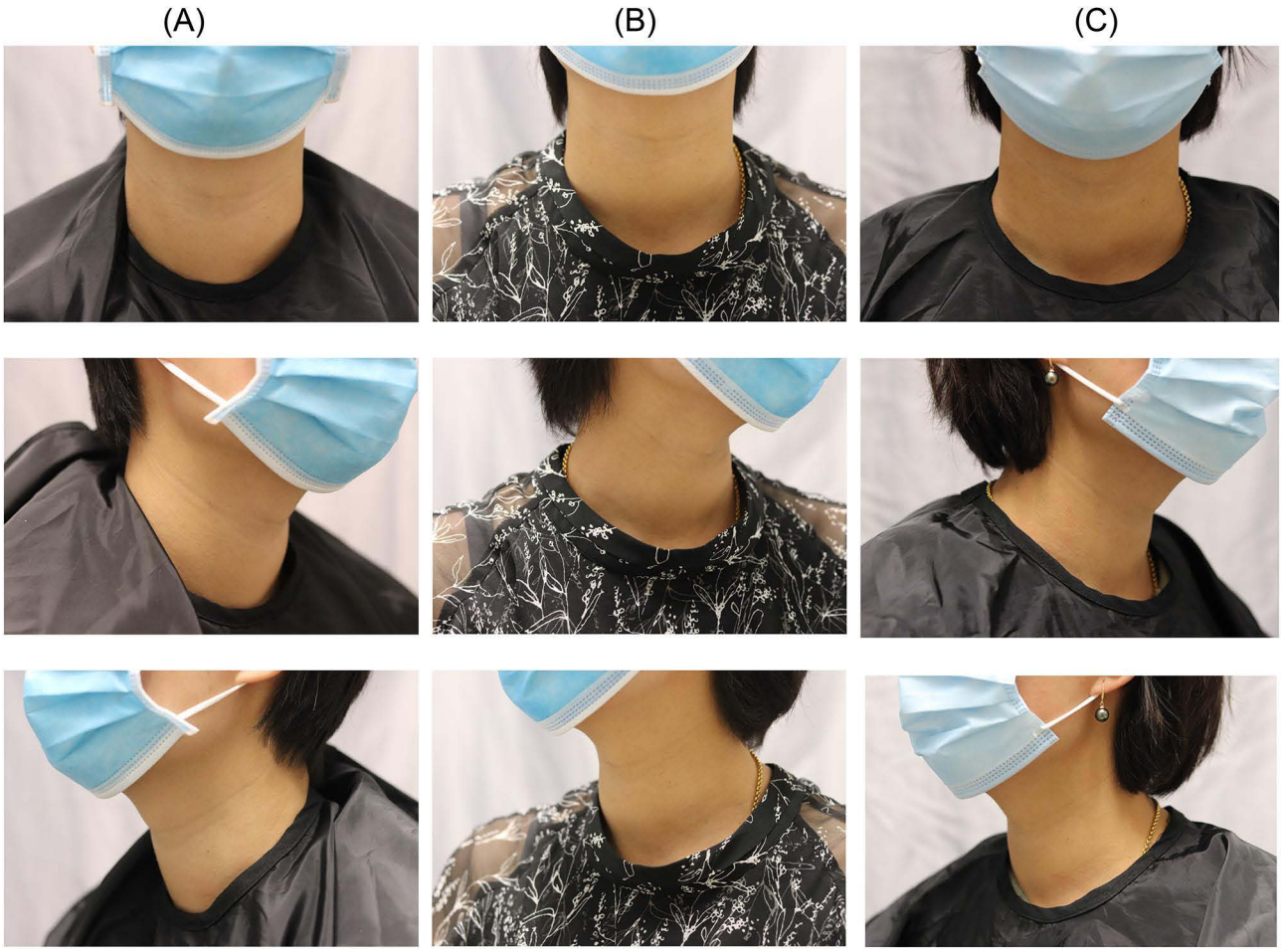

Figure 2 Representative clinical photographs of Subject 2 (experimental group) illustrating the temporal evolution of horizontal neck lines. (**A**) Baseline; (**B**) 4 weeks after the final injection (primary endpoint); (**C**) 24 weeks after the final injection. For each time point, anterior (centre), left lateral, and right lateral views are shown.

assessed by the subjects themselves at different follow-up time points, are shown in Table 3 and Figure 4. Comparison between the groups revealed no statistically significant differences ($p > 0.05$).

Safety Outcomes

Treatment-emergent adverse events (TEAEs) were limited to mild, transient injection-site bruising, swelling, pain, or erythema that resolved spontaneously within 3–7 days (Table 4). The incidence was 27.66% (26/94 patients, 52 events) in the experimental group and 40.43% (38/94 patients, 76 events) in the control group, with the majority being mild or moderate in severity. No statistically significant difference was observed in the incidence rates between the two groups ($p > 0.05$). The most frequently reported symptoms were bruising and swelling, with comparable rates between the two groups. One serious adverse event (SAE) occurred in each group (1.06% incidence, both unrelated to the device or procedure): thyroid papillary carcinoma with lymph-node metastasis in the experimental group and minimally invasive adenocarcinoma of the upper right lung in the control group. Neither the severity distribution of AEs nor their causal relationship to the investigational product differed significantly between groups. No clinically relevant changes in vital signs or laboratory parameters were observed.

Discussion

This prospective, multicenter, randomized active-controlled trial demonstrates that the experimental composite solution was non-inferior to the control product for improving moderate to severe neck wrinkles following three treatment

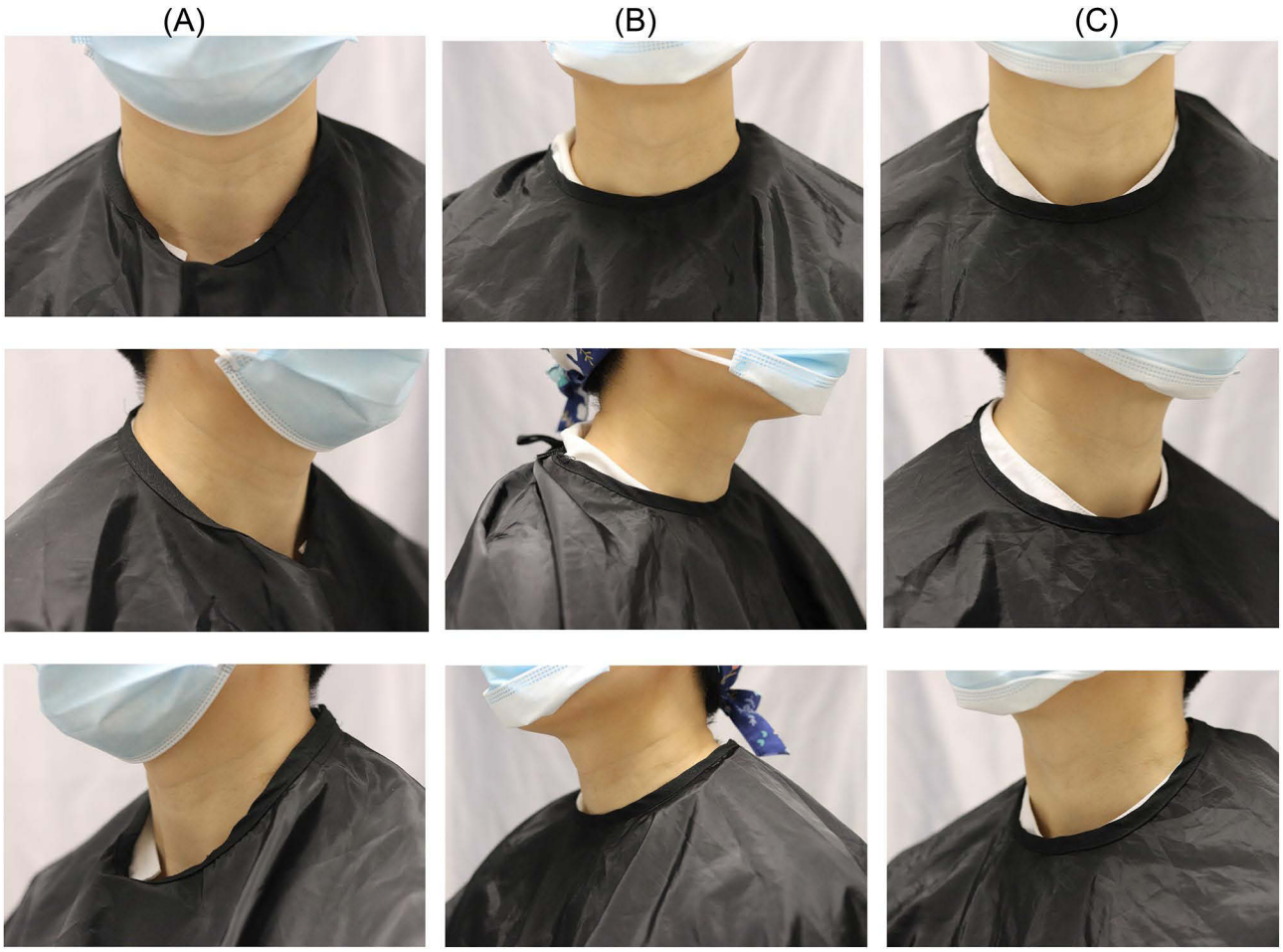

Figure 3 Representative clinical photographs of Subject 22 (control group) illustrating the temporal evolution of horizontal neck lines. (**A**) Baseline; (**B**) 4 weeks after the final injection (primary endpoint); (**C**) 24 weeks after the final injection. For each time point, anterior (centre), left lateral, and right lateral views are shown.

sessions. Moreover, both treatments exhibited a comparable and favorable safety profile, with predominantly mild and transient adverse events. The week-4 ATNLS response rate of 88.3% versus 85.1% comfortably exceeded the predefined −10% non-inferiority margin and was sustained through 24 weeks alongside all secondary endpoints. Peak improvement occurred 4 weeks after the final injection, with patient-reported GAIS scores tracking the blinded-evaluator data,

Table 3 The Subject-Assessed GAIS Responder Rate at Different Follow-Up Time Points

GAIS	Experimental Group	Control Group	P Value
Pre-dose 2			0.2035
N (missing)	94 (0)	94 (0)	
Much improved	13 (13.83%)	16 (17.02%)	
Improved	61 (64.89%)	65 (69.15%)	
Invalid	20 (21.28%)	13 (13.83%)	
Pre-dose 3			0.4508
N (missing)	94 (0)	92 (2)	
Much improved	24 (25.53%)	29 (31.52%)	
Improved	63 (67.02%)	56 (60.87%)	

(*Continued*)

Table 3 (Continued).

GAIS	Experimental Group	Control Group	P Value
Invalid	7 (7.45%)	7 (7.61%)	
Week 4 post-final injection			0.2748
N (missing)	91 (3)	89 (5)	
Very much improved	0 (0%)	1 (1.12%)	
Much improved	30 (32.97%)	34 (38.2%)	
Improved	53 (58.24%)	49 (55.06%)	
Invalid	8 (8.79%)	5 (5.62%)	
Week 12 post-final injection			0.6559
N (missing)	90 (4)	90 (4)	
Very much improved	0 (0%)	1 (1.11%)	
Much improved	24 (26.67%)	21 (23.33%)	
Improved	55 (61.11%)	63 (70%)	
Invalid	11 (12.22%)	5 (5.56%)	
Week 24 post-final injection			0.2259
N (missing)	87 (7)	89 (5)	
Very much improved	1 (1.15%)	1 (1.12%)	
Much improved	21 (24.14%)	22 (24.72%)	
Improved	49 (56.32%)	60 (67.42%)	
Invalid	16 (18.39%)	6 (6.74%)	

confirming consistent aesthetic benefit. The experimental group was numerically better tolerated compared to the control group (27.7% vs 40.4% TEAEs), although the difference did not reach statistical significance. All events were mild, transient injection-site reactions (erythema, oedema, bruising), and only one unrelated SAE occurred in each group.

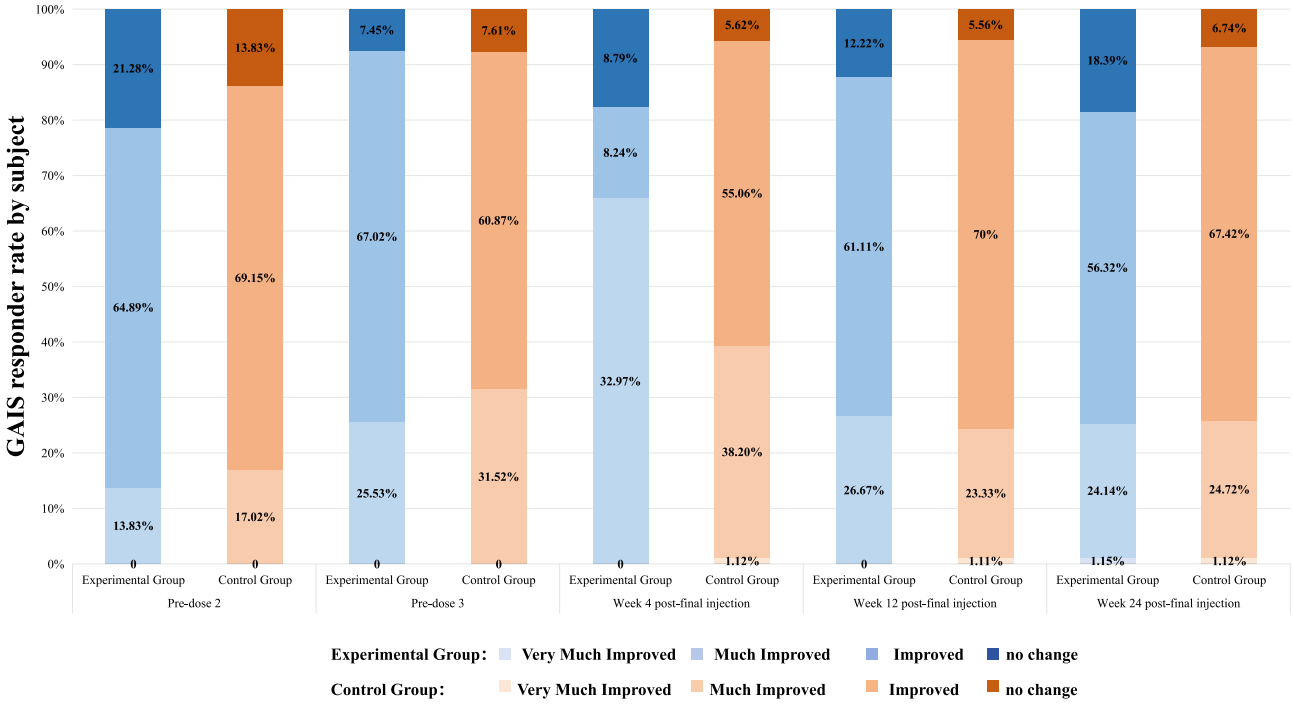

Figure 4 Comparison of GAIS responder rates between the two groups at different time points based on subject self-assessment.

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Table 4 Summary of Adverse Events

Adverse Event	Experimental Group N = 94	Control Group (N = 94)	P Value
	52 Cases	76 Cases	
TEAE	26 (27.66%)	38 (40.43%)	0.0648
Intensity of TEAEs			
Mild	44 (84.62%)	60 (78.95%)	
Moderate	7 (13.46%)	15 (19.74%)	
Severe	1 (1.92%)	1 (1.32%)	
TEAEs recorded			
Injection site bruising	29 (55.77%)	44 (57.89%)	
Injection site swelling	13 (25.00%)	26 (34.21%)	
Injection site pain	4 (7.69%)	1 (1.32%)	
Itching	5 (9.62)	3 (3.95%)	
Redness	1 (1.92%)	2 (2.63%)	
SAE	1 (1.06%)	1 (1.06%)	–
SADR	0	0	–

Abbreviations: TEAE, treatment-emergent adverse; SAE, severe adverse event; SADR, serious adverse device reaction.

Contemporary models of neck ageing extend beyond collagen/elastin loss to include depletion of the intercellular hyaluronic acid matrix, even when the dermal scaffold is morphologically intact.[17] Hyaluronic acid, a polysaccharide naturally present in human skin, plays a vital role in maintaining skin hydration, providing nutrition, and combating aging.[18] Mesotherapy, a subcutaneous injection technique pioneered by French Dr. Michel Pistor in 1952, has progressively expanded its applications in recent years to include aesthetic medicine, particularly in wrinkle improvement and facial rejuvenation.[19] The procedure involves microinjections of key therapeutic substances such as hyaluronic acid, vitamins, minerals, and amino acids, targeting the superficial papillary dermis. Drawing on this principle, the medical aesthetics market has spurred the introduction of a wide array of HA-based products since the 1980s.[20] Our findings align with published studies of non-cross-linked HA fillers for cervical rhytides, which report response rates of 80–90% and effect durations of 3–6 months.[21,22] The observed peak at week 4 and gradual decline thereafter mirrors the natural integration and resorption kinetics of non-cross-linked HA.

The experimental product embodies the mesotherapy concept: 5 mg/mL non-cross-linked sodium hyaluronate is combined with the proprietary complex (14 vitamins, 24 amino acids, 6 minerals, 5 nucleotides, 6 co-enzymes, 6 miscellaneous actives). The active comparator, approved as a Class III medical device in China in 2016, is composed primarily of sodium hyaluronate, L-carnosine, glycine, alanine, proline, and vitamin B2. It has also been shown to be safe and effective based on market feedback and published literature.[21,23] In terms of the primary endpoint, this study successfully demonstrated the non-inferiority of the investigational product to the control, as assessed by the ATNLS improvement rate. Although the difference in efficacy (88.3% vs. 85.11%) was not statistically significant, the numerically higher response rate observed with the investigational product is clinically noteworthy. While the specific contribution of individual components to the observed clinical effects cannot be definitively established from this study, the formulation is designed to augment hydration, support antioxidant defenses, and potentially influence fibroblast activity, thereby targeting skin quality beyond mechanical filling alone.[14,24–26] This conceptual framework is supported by recent multimodal imaging studies of intradermal non-cross-linked HA biorejuvenation, which have demonstrated microstructural remodeling, increased epidermal thickness, and improved skin texture using VISIA, PRIMOS 3D, and LC-OCT technologies.[27] These objective findings provide evidence-based support for dermal regeneration effects that extend beyond hydration, offering a plausible mechanistic context for the clinical improvements observed in the present study.

Additionally, it is important to contextualize these findings within the broader landscape of neck rejuvenation modalities.[28] This study demonstrates that intradermal injection of non-cross-linked HA achieves neck rejuvenation primarily through improving skin quality rather than structural volumization, offering a complementary approach to

radiofrequency/lasers, diluted CaHA, and botulinum toxin, and is best suited for patients with moderate-to-severe wrinkles without significant soft tissue ptosis or muscle hyperactivity, serving as either a standalone treatment or adjunctive procedure. However, most injectable HA evidence derives from facial indications; high-quality, active-controlled data specific to horizontal neck lines remain scarce. By adopting a rigorous non-inferiority design and standardised ATNLS photonumeric scale, the present study supplies clinicians with reliable evidence for an effective, well-tolerated therapeutic option in an anatomical region that is notoriously difficult to treat.

Several limitations should be considered. The 24-week follow-up period, while sufficient to establish mid-term efficacy, does not capture the long-term duration of effect. Future studies with extended follow-up are warranted. Secondly, given the non-superior efficacy demonstrated in this study, practical considerations such as product cost and accessibility become relevant factors for clinical decision-making and should be evaluated alongside efficacy data. Future comparative effectiveness research should incorporate formal cost-effectiveness analyses. Furthermore, the generalizability of our findings may be limited to specific patient populations, such as those with moderate to severe neck wrinkles. Future studies would benefit from including a larger and more diverse cohort, encompassing a broader spectrum of wrinkle severity, to allow for a comprehensive assessment of efficacy. Finally, the absence of pharmacokinetic or mechanistic biomarkers makes it impossible to directly attribute the observed benefits to individual components of the experimental formulation. Future translational work should correlate clinical outcome with dermal HA content, collagen turnover, and fibroblast gene-expression signatures.

Conclusion

This study demonstrates that the experimental product is non-inferior to an active comparator for improving moderate-to-severe horizontal neck lines, achieving comparable response rates (88.3% vs. 85.1% at week 4) that was sustained through 24 weeks. Both treatments exhibited favourable safety profiles and high patient satisfaction, supporting the adoption of either therapeutic option in routine neck rejuvenation practice. By providing high-quality evidence from a rigorously designed randomized controlled trial, our study addresses a critical gap in the literature and expands the therapeutic options for this challenging anatomical region. Future research should focus on long-term durability and combination strategies to optimise outcomes.

Data Sharing Statement

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

Ethical Statement

This study was approved by the Ethics Committee of Beijing Friendship Hospital, Capital Medical University (No. 2020-P1-Device-012-02) and was registered in the Chinese Clinical Trial Registry (ChiCTR2100045588).

Informed Consent

Informed consent was obtained from all volunteers.

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Disclosure

None of the authors declare competing financial or non-financial interests beyond the funding described in this work.

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