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Efficacy and safety of small-particle cross-linked hyaluronic acid intradermal injection for improving facial skin quality: a retrospective real-world study

Chungyung Keung#, Qinyang Li#, Jianxun Mao, Shunnv Jin, Yuanyuan Lin, Qing Li

Rongyue Medical Aesthetic Clinic, Shenzhen 518022, Guangdong, China.
#These authors contributed equally to this work.

Correspondence to: Dr. Chungyung Keung, MSc, Rongyue Medical Aesthetic Clinic, Shenzhen 518022, Guangdong, China.
E-mail: chungyung_keung@163.com

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Abstract

Objective: To evaluate the efficacy and safety of intradermal Small-particle cross-linked hyaluronic acid (SPCLHA) injection for improving facial skin texture and appearance in a real-world study in a Chinese population.

Methods: The SPCLHA injection has been used to improve skin texture on the face, neck, chest, and dorsal hands. However, real-world efficacy and safety evidence for the facial injection of SPCLHA for skin improvement is limited in China. We retrospectively reviewed electronic medical records to collect real-world data from participants who received at least two facial intradermal injections of SPCLHA at a Chinese clinic. The skin quality of participants was evaluated at pre-injection and after each injection using the Global Aesthetic Improvement Scale (GAIS) and the Global Photoaging Score (GPS). Safety was measured by monitoring the occurrence of adverse events. We also evaluated participant's satisfaction through surveys.

Results: The study included 39 female participants with an average age of 38.7 years, all of whom received at least three injections. Data for the first two injections were available for all participants, and 21 participants had data for the third injection. We observed a significant increase in the proportion of participants achieving the highest GAIS score, with 2.6% after the first injection, 28.2% after the second injection, and 42.9% after the third injection. Trends in the GPS scores also showed a decrease in the severity of photodamaged skin. The distribution of GPS scores was significantly different from the second injection to the pre-injection (P = 0.003), indicating fewer

participants had high GPS scores after the injections. No adverse events were reported during the study period, and 94.9% of participants were satisfied with the effects.

Conclusion: This real-world study showed that the intradermal injection of SPCLHA was effective in improving facial skin texture and appearance, and was found to be safe for use in the real-world Chinese population.

Keywords: Skin barrier, skin physiology/structure, formulation/stability, small-particle cross-linked hyaluronic acid, skin quality

BACKGROUND

Hyaluronic acid (HA), a naturally occurring polysaccharide in human tissues, effectively binds and retains water molecules[1-3]. This unique moisturizing property makes HA highly valuable in the cosmetic applications, both as skin care products and injectable fillers[4-9]. HA injections have been commonly used as soft-tissue fillers, especially for anti-wrinkle and tissue volumization, with several studies demonstrating its safety and efficacy[10-13]. While HA products enjoy global recognition for tissue filling, Asian consumers show particular interest in treatments that improve overall skin quality, including smoothness, brightness, and youthful appearance[14].

Notably, conventional hyaluronic acid (HA) formulations - including non-cross-linked HA (NCLHA) and large-particle cross-linked HA (LPCLHA) - face inherent limitations in addressing the comprehensive facial skin quality needs of Asian consumers due to their structural and functional constraints. NCLHA, despite its biocompatibility, undergoes rapid catabolism by endogenous hyaluronidases. This produces transient moisturizing effects (typically 1-2 weeks) insufficient to address persistent concerns such as fine photodamage, texture irregularities, or compromised skin barrier function. Moreover, it fails to maintain the prolonged dermal hydration necessary to modulate fibroblast behavior[4,15]. In contrast, LPCLHA is designed specifically for deep soft-tissue volumization (e.g., correction of nasolabial folds or facial contouring) and demonstrates poor permeability into the superficial-to-middle dermis[15,16]. This anatomical restriction prevents it from targeting key drivers of skin quality - dermal hydration retention, fibroblast activation, and dermal-epidermal junction (DEJ) integrity - and also limits its ability to stimulate neo-collagenesis or dermal vascularization, processes critical for reversing photoaging-related structural changes[17-21].

In response to these challenges, small-particle cross-linked hyaluronic acid (SPCLHA) has emerged as a tailored solution that utilizes its distinct structural and physical properties to overcome these constraints. Its cross-linked matrix slows enzymatic degradation, extending residence time in the dermis to 4-8 weeks[18,22]. Additionally, its small particle size facilitates precise intradermal delivery (via 32-gauge needle) to the superficial-to-middle dermis, a region critical for skin quality regulation. This targeted localization directly interacts with fibroblasts and the DEJ, initiating a cascade of beneficial physiological responses: DEJ reconstruction to strengthen skin barrier function[19], induction of neo-collagenesis to reduce fine wrinkles[18], and promotion of dermal vascularization to enhance cutaneous blood perfusion and brightness[21]. Collectively, these properties enable SPCLHA to deliver comprehensive skin quality improvement, extending beyond the isolated moisturization or volumization offered by conventional HA formulations.

SPCLHA injection has obtained regulatory approval in China and other countries for skin rejuvenation, restoring skin hydrobalance, and improving skin structure and elasticity[15,16,22]. Chinese expert consensus

recommends SPCLHA intradermal injection for enhancing skin texture across multiple areas, including the face, neck, chest, and dorsal hands[17]. However, China's National Medical Products Administration currently limits SPCLHA injection approval to hand rejuvenation[23]. Despite the strong demand for facial skin improvement among Chinese consumers, real-world evidence supporting SPCLHA injection's efficacy for facial enhancement remains limited.

The present study aims to evaluate the efficacy and safety of SPCLHA intradermal injections for facial skin appearance improvement in the Chinese population through retrospective analysis in a real-world setting.

METHODS AND MATERIALS

Study design and data collection

We conducted a non-interventional, retrospective, single-arm study at Rongyue Medical Aesthetic Clinic (Shenzhen, China). Data collection spanned from June 1, 2020 to January 31, 2023, encompassing measurements obtained at baseline (pre-injection) and at each subsequent visit prior to the following injection. Owing to the retrospective, real-world design of this study, post-injection follow-up visits were not governed by a rigid research protocol. Rather, appointment scheduling emerged from collaborative discussions between participants and clinicians, mirroring the flexible approach typical of aesthetic clinic operations. Assessment of each prior injection drew upon measurements taken immediately before the subsequent injection.

Participants and materials

Inclusion criteria

The study enrolled Chinese individuals meeting the following criteria (1) age between 18 years and 65 years, (2) receipt of at least two facial intradermal SPCLHA injections at the study clinic during the period from June 1, 2020, to January 31, 2023, (3) Fitzpatrick skin phototype I through IV[24], and (4) presentation of undesirable facial skin appearance (such as dry, rough, photoaged skin or wrinkles) complained by the participants or diagnosed by the physicians.

Exclusion criteria

We excluded individuals with allergies to HA, pregnancy, lactation, active dermatological conditions (e.g., infection, eczema, dermatitis, psoriasis, acne, rosacea), autoimmune disorders or malignancies.

SPCLHA intradermal injections

Microinjections of 2mL undiluted SPCLHA (Galderma; Uppsala, Sweden) were administered into the deep dermis of facial skin using a 32-gauge needle, with 20-μL aliquots delivered per injection site at 1-cm intervals. Topical anesthesia was achieved through application of 5% lidocaine ointment to the entire facial area at least 30 min before SPCLHA injection. Participants were recommended to receive injections at 0, 4, and 8 weeks. Actual injection intervals observed in clinical practice are detailed in Section **Patient characteristics**. Follow-up injections were subject to adjustment based on the participants' facial skin condition.

Ethics approval

This study adhered to the Guidelines for Exemption from Ethical Review for Medical and Health Institutions in Guangdong Province (Trial) and the Personal Information Protection Law of the People's Republic of China, satisfying criteria for ethical review exemption as follows:

Table 1. Scoring criteria for GAIS

GPS score	Desciption
-1	Worsened
0	No change
1	Improved
2	Much improved
3	Very much improved

GAIS: Global Aesthetic Improvement Scale; GPS: global photoaging score.

(1) Data anonymization: All information was extracted from historical medical records and anonymized (removal of personal identifiers such as names/identification numbers), avoiding privacy-related ethical concerns.

(2) No additional risks: The study relied exclusively on pre-existing data, with no direct participant contact, extra interventions, or infringement upon participant rights - conforming to "low-risk" classification standards.

(3) Alignment with Public interest: The findings furnish evidence to inform clinical aesthetic practice, with discernible societal and academic value.

Formal ethical approval was not mandated under applicable local regulations.

Informed consent

Written informed consent was obtained from all participants for:

(1) Utilization of their de-identified clinical data in this retrospective study;

(2) Publication of facial photographs and clinical details (where applicable).

Study outcomes

Real-world efficacy was evaluated through facial photographs assessed by an independent dermatologist using the Global Aesthetic Improvement Scale (GAIS) and the Global Photoaging Score (GPS) [Tables 1 and 2][25,26]. Photographs were taken at pre-injection (before the 1st injection) and at each subsequent visit prior to the next injection. Efficacy at each timepoint was assessed by comparing photographs from consecutive visits. The final injection session was excluded from evaluation due to the absence of follow-up photographs.

The GAIS uses a 5-point scale (-1 to 3) to quantify aesthetic improvement, wherein scores of 1 to 3 reflect varying levels of skin improvement (from "improved" to "very much improved"), whereas scores of 0 and -1 indicate no change or worsening [Table 1][25]. GAIS scores were assigned by comparing photos to assess inter-injection changes. The GPS also uses a 5-point scale (0 to 4), with higher scores indicating more severe photodamage, including wrinkles, roughness, and dyspigmentation[Table 2][26]. The primary efficacy endpoint was the percentage of participants achieving a GAIS score ≥ 1 (indicating improvement) after the second injection. Secondary endpoints included GAIS scores after the first and third injections, GPS scores after each injection, and overall trends in these scores during the study.

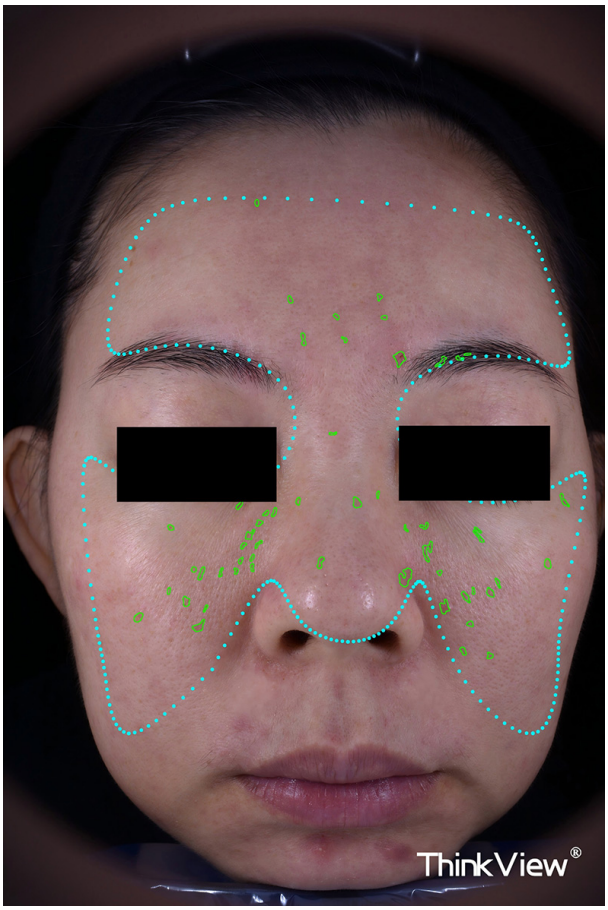

Figure 1. Demonstration of facial front-view analysis area of the ThinkView camera system

Table 2. Scoring criteria for GPS

GPS score	Desciption
0	Facial skin is smooth to the touch, without significant fine lines or unevenness in pigmentation in any areas (cheeks, forehead, and the perioral area)
1	Facial skin shows 1 area (cheeks, forehead, or the perioral area) of significant roughness, dyspigmentation (hypopigmentation or hyperpigmentation), or fine lines
2	Facial skin shows 2 areas (cheeks, forehead, or the perioral area) of significant roughness, dyspigmentation (hypopigmentation or hyperpigmentation), or fine lines, or shows roughness, dyspigmentation, and fine lines in 1 area
3	Facial skin shows 3 areas (cheeks, forehead, or the perioral area) of significant roughness, dyspigmentation (hypopigmentation or hyperpigmentation), or fine lines, or shows roughness, dyspigmentation, and fine lines in 2 areas
4	Facial skin shows any degree of photodamage greater than 3

GPS: Global photoaging Score.

Objective skin quality assessment was conducted using a digital photography system (CBS software integrated with the ThinkView® camera system) capable of capturing facial images under multiple light spectrums: parallel-polarized, cross-polarized, and near-infrared light. The analytical region encompassed the forehead, nasal area, and bilateral cheeks (Figure 1, used with participant consent), yielding quantitative scores for ultraviolet (UV) spots, wrinkles, and red areas. Lower scores indicated improvement in these skin parameters following SPCLHA injection. The analytical precision of this system has been validated, with previous studies reporting 84.40% accuracy for pore detection[27,28]. These device-based measurements provide objective data that complement GAIS and GPS assessments, offering quantifiable metrics for specific skin quality parameters that may not be captured by general assessment scales.

For safety assessment, the incidence of adverse events that occurred throughout the study period was documented. Patient satisfaction was evaluated through survey completed after each injection, wherein participants rated their satisfaction as "very satisfied", "satisfied" or "not satisfied" and provided written feedback. Overall satisfaction was determined based on each participant's final survey response. Given the diverse aesthetic concerns of participants at pre-injection, subgroup analyses were conducted based on their primary skin complaints or issues: UV spots/hyperpigmentation, red areas, wrinkles and dullness. Each subgroup was evaluated using corresponding ThinkView camera system measurements specific to their primary concern. Notably, participants could belong to multiple subgroups concurrently owing to the presence of multiple skin complaints at pre-injection.

Statistical analysis

Statistical analyses were performed for the overall cohort (i.e. all included participants) and three subgroups using R software version 4.2.1 Normality of continuous variables was assessed using the Shapiro-Wilk test. Based on the distribution characteristics, continuous variables were described as median (interquartile range, IQR) for non-normally distributed data or mean (± standard deviation [SD]) for normally distributed data. Categorical variables were expressed as frequencies and percentages. GAIS and GPS were treated as categorical variables with four levels when describing their distributions in participants, and as continuous variables when describing the trends of the scores over time.

For comparisons of GAIS and GPS changes after each SPCLHA injection, the Wilcoxon signed-rank test was used, as these scores were treated as ordinal/continuous variables and differences between paired measurements may not follow a normal distribution. For objective skin analysis parameters (UV spots, pores, porphyrins, wrinkles, red areas, and brown areas), linear mixed models (LMMs) were used to evaluate changes across treatment timepoints. The LMM was specified with the following structure: Value ~ Timepoint + (ParticipantID), where "Value" represents the outcome measure, "Timepoint" is the fixed effect of measurement occasion (baseline, 1st, 2nd, or 3rd injection), and "(ParticipantID)" represents the random intercept for each participant. The restricted maximum likelihood (REML) estimation method was used for parameter estimation. Significance of the time effect was evaluated using Wald chi-square tests. When the overall time effect was significant ($P < 0.05$), post hoc pairwise comparisons were conducted using Wilcoxon signed-rank tests with Bonferroni correction for multiple comparisons.

Missing data were handled using the complete case analysis approach, whereby participants with missing values for any analyzed variables were excluded from the specific analysis. A two-sided P-value < 0.05 was considered statistically significant for all analyses.

RESULTS

Patient characteristics

Of 160 participants who underwent SPCLHA injection during the study period, 39 completed a second visit and satisfied the eligibility criteria for analysis. All participants were female, with a mean age 38.7 years and Fitzpatrick skin types II-IV. At pre-injection, GPS scores of 3 were recorded in 59% of participants, while 33.3% presented with a score of 2. Notably, nearly half of the cohort (46.2%) had previously undergone other cosmetic procedures. Participants commonly reported concerns regarding dullness, UV spots, reddening, and wrinkles. The mean injection intervals were 42.7 days (SD 14.0) between the first and second treatments, 50.0 days (SD 33.2) between the second and third, and 90.5 days (SD 42.8) between the third and fourth. A summary of the participant characteristics is presented in Table 3.

Table 3. Participant characteristics

	Characteristics	Overall (*N* = 39)
Age, mean (± SD)		38.74 (7.92)
Sex, N (%)		
	Female	39 (100)
Ethnicity, N (%)		
	Han Chinese	37 (94.9)
	Unknown	2 (5.1)
Skin issues, N (%)		
	Dullness	33 (84.6)
	Dark spot UV Spots/Hyperpigmentation	15 (38.5)
	Reddening	23 (59)
	Wrinkles	21 (53.8)
Fitzpatrick skin type, N (%)		
	Type I	0 (0)
	Type II	9 (23.1)
	Type III	21 (53.8)
	Type IV	9 (23.1)
Injection Intervals, Days		
	1st and 2nd treatments	42.7（14.0）
	2nd and 3rd treatments	50.0（33.2）
	3rd and 4th treatments	90.5（42.8）
History of cosmetic procedures, N (%)		18 (46.2)
	HA filler	4 (10.3)
	Botulinum toxin injection	6 (15.4)
	Radiofrequency	4 (10.3)
	Laser	13 (33.3)
	Collagen filler	1 (2.6)
GPS, N (%)		
	1	1 (2.6)
	2	13 (33.3)
	3	23 (59)
	4	2 (5.1)

GPS: Global photoaging score; GAIA: HA: hyaluronic acid; SD: standard deviation; UV: ultraviolet.

Efficacy outcome

All 39 participants completed a minimum of three injections; however, only 21 (53.9%) returned for the fourth injection. The primary efficacy endpoint was successfully met, as every participant (100%, 39/39) exhibited improvement (GAIS score ≥ 1) following both the first and second treatments. Sequential analysis of GAIS scores revealed significant improvement between consecutive treatments (first to second treatment: $P < 0.001$; second to third treatment: $P < 0.001$).The proportion of participants achieving substantial improvement (GAIS score 3) rose progressively from 2.6% (1/39) after the initial treatment to 28.2% (11/39) following the second and further to 42.9% (9/21) after the third. GPS scores also demonstrated significant improvement from pre-injection to the second treatment ($P = 0.003$), characterized by a decline in severe photodamage (GPS Score 3) from 59% (23/39) to 33.3% (13/39),

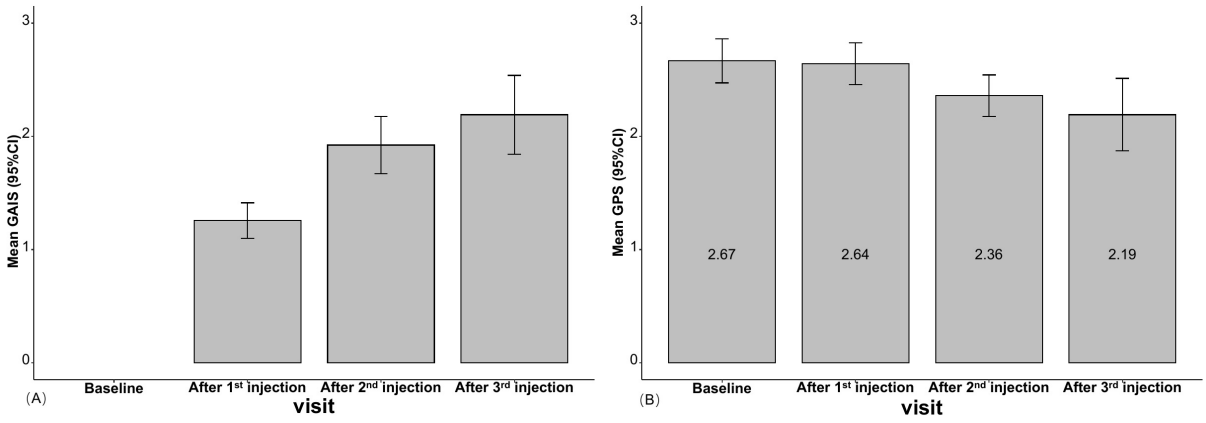

Figure 2. Trends in mean GAIS (A) and GPS (B) from pre-injection to after the third injection in the overall group. GAIS: Global Aesthetic Improvement Scale; GPS: global photoaging scale.

Table 4. GAIS and GPS evaluation at pre-injection and after the first, second, and third SPCLHA injection

Assessment tool	Pre-injection *N* = 39	After first injection *N* = 39	After second injection *N* = 39	After third injection *N* = 21
GAIS, n (%)				
-1	-	0 (0)	0 (0)	0 (0)
0	-	0 (0)	0 (0)	0(0)
1	-	30 (76.9)	14 (35.9)	5 (23.8)
2	-	8 (20.5)	14 (35.9)	7 (33.3)
3	-	1 (2.6)	11 (28.2)	9 (42.9)
P-value	-	-	<0.001*	<0.001*
GPS, n (%)				
1	1 (2.6)	1 (2.6)	1 (2.6)	3 (14.3)
2	13 (33.3)	13 (33.3)	24 (61.5)	12 (57.1)
3	23 (59)	24 (61.5)	13 (33.3)	5 (23.8)
4	2 (5.1)	1 (2.6)	1 (2.6)	1 (4.8)
P-value	-	0.773	0.003*	0.006*

There is no pre-injection GAIS score since the tool evaluated aesthetic improvement concerning the previous injection. A GAIS score of 1 or more represents improved skin quality.*Wilcoxon signed-rank test was performed and $P < 0.05$ indicates a statistically significant difference between each injection and the pre-injection. GAIS: Global Aesthetic Improvement Scale; GPS: global photoaging scale; SPCLHA: Small-particle cross-linked hyaluronic acid.

accompanied by a rise in moderate photodamage (GPS Score 2) from 33.3% (13/39) to 61.5% (24/39). The comprehensive distribution of GAIS and GPS scores is detailed in Table 4, with temporal trends in mean scores depicted in Figure 2.

Device-based skin analysis, however, failed to demonstrate significant improvements in overall skin appearance indices following each injection relative to the preceding assessment. As shown in Table 5, red area scores exhibited considerable variability across treatment timepoints (LMM time effect: $P = 0.001$), with mean scores fluctuating from 552.67 ± 544.88 at pre-injection to 470.39 ± 514.86 after the first injection, 592.41 ± 546.99 after the second, and 927.40 ± 637.99 after the third. Post hoc pairwise comparisons revealed significant differences between baseline and first injection ($P = 0.003$), baseline and third injection ($P = 0.038$), first and second injection ($P = 0.021$), and first and third injection ($P = 0.003$).

Table 5. Linear mixed model analysis of device-based skin parameters across treatment timepoints

Parameter	Baseline (*n* = 39)	1st Injection (*n* = 39)	2nd Injection (*n* = 39)	3rd Injection (*n* = 21)	LMM time effect *P*-value	Post hoc comparisons
UV spots	208.76 ± 142.24	200.25 ± 148.36	204.88 ± 158.42	206.71 ± 156.87	0.812	-
Pores	4,111.67 ± 1,599.44	3,785.15 ± 1,862.62	4,235.49 ± 2,292.78	4,884.33 ± 1,920.81	0.189	Baseline *vs.* 3rd: 0.020*
Porphyrins	1,131.59 ± 1,874.69	930.64 ± 2,237.15	1,284.46 ± 3,480.99	1,003.10 ± 1,674.65	0.645	-
Wrinkles	4,977.18 ± 1,208.54	4,719.46 ± 1,366.12	4,791.56 ± 1,448.05	5,144.55 ± 1,251.66	0.815	-
Red area	552.67 ± 544.88	470.39 ± 514.86	592.41 ± 546.99	927.40 ± 637.99	0.001	Baseline *vs.* 1st: 0.003 Baseline *vs.* 3rd: 0.038 1st *vs.* 2nd: 0.021 1st *vs.* 3rd: 0.003
Brown area	1019.95 ± 1191.08	948.82 ± 667.57	1191.35 ± 806.79	1150.09 ± 692.82	0.506	-

*Data presented as mean ± SD. * $P < 0.05$, ** $P < 0.01$. LMM: Linear Mixed Model; UV: ultraviolet.

Table 6. Device-based skin analysis results in four subgroups

Skin appearance score	Pre-injection	After 1st injection	After 2nd injection	After 3rd injection	*P*-value*
Subgroup with UV spots at pre-injection	*N* = 15	*N* = 15	*N* = 15	*N* = 8	
UV spot, mean (± SD)	247.09 (157.86)	198.47 (115.66)	204.88 (131.14)	213.15 (129.26)	0.765
Wrinkles, mean (± SD)	4,745.50 (1,437.64)	4,680.29 (1,514.94)	5,078.36 (1,546.58)	4,862.00 (1,249.55)	0.887
Red area, mean (± SD)	694.09 (684.80)	572.07 (649.61)	748.47 (661.87)	1,068.34 (745.92)	0.422
Subgroup with red areas at pre-injection	*N* = 23	*N* = 23	*N* = 23	*N* = 12	
UV spot, mean (± SD)	191.06 (160.90)	170.03 (154.39)	178.61 (156.31)	159.40 (129.24)	0.940
Wrinkles, mean (± SD)	4,827.48 (1,098.14)	4,897.63 (1,138.45)	4,912.42 (1,207.10)	5,194.50 (1,214.85)	0.843
Red area, mean (± SD)	737.08 (626.82)	637.80 (600.71)	657.37 (596.79)	1,001.56 (766.24)	0.398
Subgroup with Wrinkless at pre-injection	N = 21	N = 21	N = 21	N = 13	
UV spot, mean (± SD)	224.13 (138.27)	208.34 (114.09)	217.78 (151.31)	267.51 (164.62)	0.675
Wrinkles, mean (± SD)	5,061.17 (1,274.93)	4,800.80 (1,300.57)	5,048.45 (1,460.66)	4,798.76 (1,288.37)	0.877
Red area, mean (± SD)	572.21 (595.55)	579.08 (636.17)	796.24 (615.31)	1,076.13 (670.65)	0.089
Subgroup with dullness at pre-injection	N = 33	N = 33	N = 33	N = 18	
UV spot, mean (± SD)	220.74 (148.71)	215.33 (154.78)	219.91 (167.04)	224.84 (162.59)	0.997
Wrinkles, mean (± SD)	5,105.86 (1,224.81)	4,742.35 (1,410.22)	4,821.45 (1,520.33)	5,337.42 (1,155.50)	0.401
Red area, mean (± SD)	523.96 (551.02)	494.86 (552.51)	621.46 (584.97)	1,003.26 (651.70)	0.019

*One-way ANOVA was performed and $P < 0.05$ indicates a statistically significant difference between each injection and pre-injection.SD: standard deviation; UV: ultraviolet.

Four subgroups were stratified based on participant's complaints at baseline - UV spots, redness, wrinkles and dullness - to examine trends in their mean ThinkView measurements [Table 6]. Each subgroup initially showed improvement in their respective ThinkView measurements following the first injection, though these changes did not reach statistical significance throughout the study duration.

Representative photographic documentation using multiple light spectra demonstrates the clinical improvements in facial appearance achieved with SPCLHA treatment. Figure 3 illustrates the reduction in red areas after the first and second injections, while Figures 4 and 5 show improvements in hyperpigmentation and wrinkles compared to pre-injection.

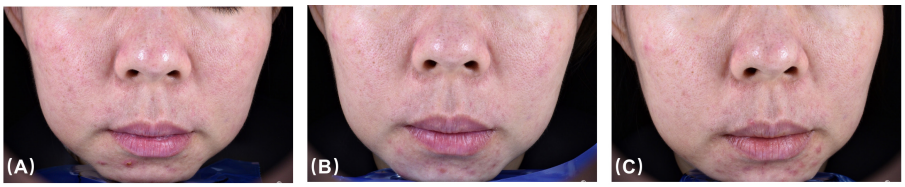

Figure 3. A 35-year-old female participant received two sessions of injections. Images show facial skin redness at pre-injection (A), and changes after the first injection (B) and after the second injection (C).

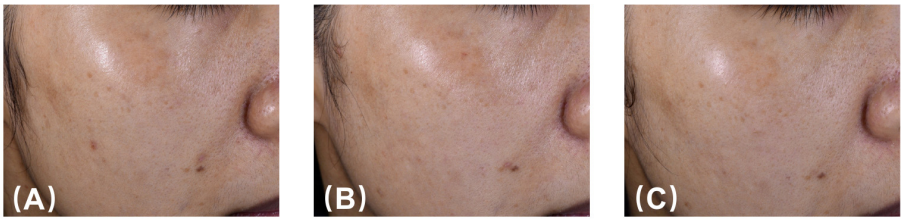

Figure 4. A 39-year-old female participant received two sessions of injections. Images show facial skin pigmentation at pre-injection (A), and changes after the first injection (B) and after the second injection (C).

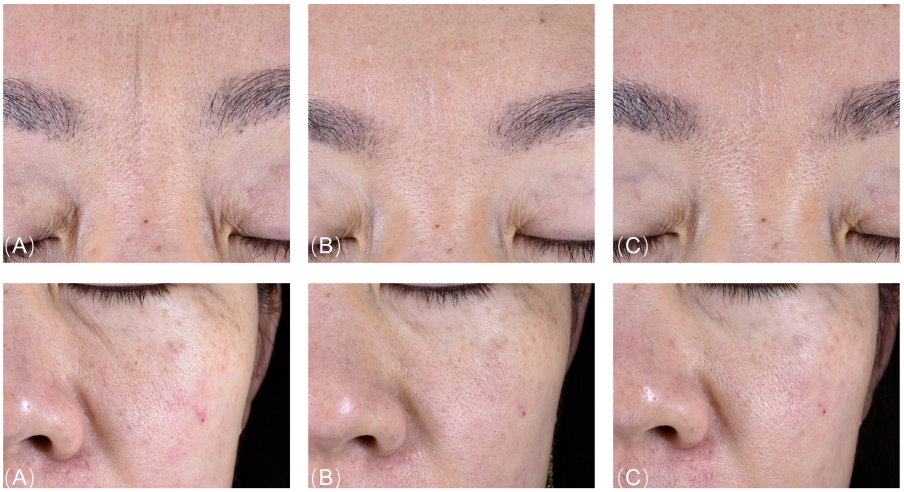

Figure 5. A 40-year-old female participant received two sessions of injections. Images show facial skin wrinkles at pre-injection (A), and changes after the first injection (B) and after the second injection (C).

Safety and satisfaction

Throughout the entire study duration, no serious adverse events were either reported by participants or observed by investigators. Treatment satisfaction assessments indicated high levels of patient satisfaction, with 94.9% of participants reporting being either satisfied (38.5%, 15/39) or very satisfied (56.4%, 22/39) with the treatment outcomes.

DISCUSSION

This real-world study assessed the effectiveness of SPCLHA intradermal injections for improving facial skin quality among Chinese participants, along with their safety profile. The main results paint a clear picture: 100% of participants showed aesthetic improvement (GAIS score ≥ 1) after the first two injections, photodamage dropped substantially (GPS score), no adverse events occurred, and patient satisfaction reached 94.9%. Taken together, these findings confirm that SPCLHA delivers genuine clinical value for facial rejuvenation in real-world settings.

The therapeutic benefits of SPCLHA arise from its structural advantages over conventional HA formulations and its specific biological effects[17-21]. Its cross-linked matrix resists enzymatic degradation, prolonging dermal retention to 4-8 weeks (compared with 1-2 weeks for NCLHA)[4,15], which allows for prolonged hydration through water molecule binding. The small particle size further enables accurate placement in the superficial-to-middle dermis via 32-gauge needles, directly engaging fibroblasts and the DEJ: it reinforces DEJ integrity to boost skin barrier function, stimulates neo-collagenesis to reduce fine wrinkles, and promotes dermal vascularization to improve skin brightness[18-21]. These multifaceted effects address persistent concerns such as dryness, roughness, and photodamage, as evidenced by the progressive increase in GAIS score 3 (from 2.6% after the first injection to 42.9% after the third) and the reduction in severe photodamage (GPS score 3: 59% pre-injection to 33.3% after the second injection). Representative case images further confirm visual improvements in redness, hyperpigmentation, and wrinkles [Figures 3-5], distinguishing SPCLHA from NCLHA (which offers only hydration) and LPCLHA (which provides only deep volumization)[15,16].

Interestingly, the ThinkView camera system (objective skin analysis) uncovered a noteworthy trend in red area scores: scores decreased slightly on average after the first injection (from 552.67 to 470.39) but rose during subsequent treatments (592.41 after the second, 927.40 after the third), with an identical pattern observed in the subgroup of participants initially reported skin redness. This variation likely reflects SPCLHA's dual impact on skin inflammation and angiogenesis: following the first injection, SPCLHA promotes keratinocyte hydration and proliferation, easing inflammation and thereby reducing redness; the later increases in redness may stem from its stimulation of dermal vascularization (a central mechanism for long-term skin brightness), given that skin redness is fundamentally tied to capillary formation[18,21]. Although this trend did not undermine the overall aesthetic gains observed in GAIS/GPS scores, it points to SPCLHA's intricate biological influence on skin microcirculation - a topic warranting deeper exploration. These mechanisms also underpin SPCLHA's potential for other skin conditions (e.g., acne scars, tear troughs)[7, 29-31], though the present study focuses specifically on facial photodamage and texture.

The safety profile of SPCLHA observed in this study aligns with the well-established tolerability of HA fillers[32]. HA enjoys widespread use in aesthetic medicine because of its biodegradability and minimal inflammatory potential; a histological investigation of cross-linked HA for lip augmentation found no tissue inflammation or contraction in treated areas[33]. In line with these observations, no treatment-related adverse events were documented during the entire treatment and follow-up period, a finding that directly addresses the growing concerns regarding complications associated with soft tissue injectable fillers[32]. Clinicians should nonetheless follow anatomical best practices (e.g., avoiding labial gland compression to prevent lumps in lip augmentation[34]), and our data affirm SPCLHA's appropriateness for routine facial skin quality improvement, bolstered by high patient satisfaction (56.4% "very satisfied", 38.5% "satisfied").

A notable real-world departure from standardized protocols surfaced: the mean interval between the first and second injections reached 42.7 days, exceeding the recommended 30 days[17]. This discrepancy may have modestly underestimated efficacy, as SPCLHA's peak therapeutic effect occurs 1-2 weeks post-injection[18], whereas our assessments were conducted immediately before subsequent treatments. Moreover, the bioabsorbable nature of SPCLHA and optional follow-up visits (only 21 of 39 participants completed a fourth injection) restricted long-term outcome assessment. Nevertheless, the progressive improvements in GAIS and GPS scores confirm SPCLHA's efficacy despite these real-world constraints.

This study addresses two critical gaps in SPCLHA research among Chinese populations. Prior Chinese studies focused on hand rejuvenation[23] or combination treatments[32], leaving a lack of evidence for facial applications - where consumer demand far exceeds Chinese National Medical Products Administration

approval (currently limited to hand rejuvenation[23]). Our work is the first retrospective analysis of SPCLHA facial injections with standardized intervals in a Chinese cohort, providing real-world data on efficacy and safety. Second, we identified discrepancies between clinical practice (e.g., extended injection intervals) and manufacturer recommendations, offering actionable insights for protocol optimization. These contributions bolster SPCLHA's prospects as an off-label option for facial skin quality improvement, pending broader regulatory clearance.

Several limitations should be considered when interpreting our findings. First, the study design was retrospective and lacked a control group, limiting our ability to establish causal relationships and compare the efficacy of SPCLHA injections to alternative treatments or placebo. Second, although the GAIS and GPS tools provided a quantitative measure, the evaluation of scores relied on subjective assessments by a single dermatological expert, which may introduce bias. We could not control for potential confounders such as exposure to sunlight, use of skin products, or concomitant cosmetic procedures that the participants may have received during the study period. Retrospective data collection, as well as a lack of follow-up visits, emphasizes the challenge of obtaining complete data for analysis. The safety outcomes could also be subject to recall bias, as participants could only report adverse events after receiving one injection at their next visit. Without adequate medical knowledge, participants may also overlook mild adverse events such as redness and swelling, or fail to associate some adverse effects with the injection. Furthermore, although the relatively modest sample size - an inherent limitation of this single-center retrospective study - may somewhat constrain the direct generalizability of our findings to wider populations, the consistent efficacy patterns and favorable safety profile observed in this study have already furnished clear preliminary evidence for SPCLHA's clinical value.

In summary, our real-world findings indicate that SPCLHA intradermal injections are both effective and safe for improving facial skin texture and photodamage in Chinese populations. For clinicians, these findings support the integration of SPCLHA into aesthetic treatment protocols, with a focus on aligning injection intervals closer to the recommended 30 days to maximize therapeutic efficacy. For the Chinese market - where demand for facial skin quality improvement remains high - this study provides critical evidence to support the potential expansion of SPCLHA's regulatory indications beyond hand rejuvenation. Looking ahead, future studies should use prospective, controlled designs with standardized outcome measures (e.g., objective ThinkView metrics) to further validate these findings, explore long-term treatment effects, and optimize personalized injection schedules. Additionally, further investigation into SPCLHA's impact on dermal angiogenesis is warranted to clarify the fluctuating redness scores observed in device-based skin analysis.

Conclusion

In conclusion, our study demonstrates that SPCLHA injections effectively and safely improve facial skin quality among Chinese participants, with results substantiated by the GAIS and GPS assessment tools. This study adds to the existing evidence and supports the clinical use of SPCLHA facial injections in this specific population. The findings have direct clinical implications for aesthetic practitioners, suggesting that SPCLHA injections could be integrated into aesthetic treatment protocols as a safe and effective option for facial skin improvement. Future research incorporating more rigorous study designs and methods could further optimize treatment protocols, potentially enabling practitioners to personalize injection intervals based on individual skin characteristics, expand applications to different facial areas, and develop combination protocols with other aesthetic treatments to maximize patient outcomes.

DECLARATIONS

Authors' contributions

Study design & Project administration: Keung C, Li Q

Clinical implementation & Data collection: Jin S, Lin Y, Li Q

Statistical analysis & Visualization: Li Q, Mao J

Manuscript writing & Revision: Keung C, Li Q, Mao J

Resources & Funding acquisition: Keung C

Supervision & Final approval: Keung C, Li Q, Mao J, Jin S, Lin Y, Li Q

Availability of data and materials

The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request.

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Conflicts of interest

This study was financially supported by Galderma (Lausanne, Switzerland). None of the authors are employees, consultants, or shareholders of Galderma. Galderma had no involvement in the study design, data collection and analysis, interpretation of results, writing of the manuscript, or decision to submit the article for publication. All other authors declare no additional conflicts of interest related to this work.

Ethical approval and consent to participate

This study was granted an exemption from requiring ethics approval by the Institutional Review Board of Rongyue Medical Aesthetic Clinic (Exemption No. RYYL-2023-01 on February 23, 2023). This study was granted ethics exemption as a non-interventional retrospective study using exclusively anonymized historical medical records, which carries no additional risks to participants, in accordance with the Guidelines for Exemption from Ethical Review for Medical and Health Institutions in Guangdong Province (Trial) and the Personal Information Protection Law of the People's Republic of China.

Consent for publication

Written informed consent was obtained from all participants for: (1) Utilization of their de-identified clinical data in this retrospective study; (2) Publication of facial photographs and clinical details (where applicable).

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