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Efficacy and Safety of Polycaprolactone in Treating Nasolabial Folds: A Prospective, Multicenter, and Randomized Controlled Trial

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Abstract

Nasolabial folds (NLFs) are the most pronounced sign of facial aging. This study explored the efficacy and safety of polycaprolactone gel in treating Chinese patients with moderate-to-severe NLFs. Patients with moderate-to-severe NLF who wished to be treated by dermal fillers were recruited from three centers between July 2017 and September 2019. The randomizing ratio was 1:1 in the polycaprolactone group (polycaprolactone injection) or control group (sodium hyaluronate gel injection). The primary endpoint was the effectiveness rate of Wrinkle Severity Rating Score (WSRS) scores at 12 months after injection. The full-analysis set (FAS) and safety sets had 80 patients in the polycaprolactone group and control group, respectively. In the FAS, the effectiveness rate at 12 months in the polycaprolactone group was 88.8% compared with 23.8% in controls ($P < 0.001$). The improvement in WSRS sustained during 12 months in the polycaprolactone group, while gradually vanished in the control group since 3 months after surgery. The global aesthetic improvement scale (GAIS) by investigator assessments was improved, much improved, or very much improved in all patients during follow-up, while the proportion of patients with a "no change" assessment gradually increased during follow-up after 6 months in the control group. The rates of injection-related adverse event (AE) and serve injection-related AE were 8.8 versus 11.3% and 0 versus 1.3% in the polycaprolactone group and control groups, respectively. Polycaprolactone gel injection is effective and safe to treat moderate-to-severe NLFs in Chinese patients.

Keywords
- nasolabial fold
- aesthetic
- dermal filler
- facial wrinkles
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Nasolabial folds (NLFs) are defined by facial structures that support the buccal fat pad, and they separate the cheeks from the upper lip.[1,2] Aging can increase the NLF length and depth.[3] Prominent NLFs are caused by the reduction of deep adipose tissues and collagen and the subsequent reduction of midface muscle contour, resulting in wrinkles and folds.[3] The aging of facial features can be very distressing to many individuals.[4]

Even if rhytidectomy is considered a safe procedure, it carries risks of hematoma, skin necrosis, nerve injury, infection, and scarring,[5] and these risks, even if minimal, deter many patients from undergoing surgery to correct NLFs. Therefore, in the past several decades, dermal filler injection has been widely applied to facial wrinkles correction.[6–9] In 2018 alone, 2,671,130 dermal injection procedures were performed in the United States, showing a 39% increase since 2013.[10] Although dermal fillers are classified as permanent and nonpermanent,[11,12] they are generally considered safe but delayed reactions can occur.[13] Permanent fillers are not recommended in many countries, but nonpermanent fillers require repeated injections.[11,12] Nevertheless, starting in the 2000s, a new generation of dermal fillers was developed, known as collagen stimulators, characterized by increased collagen content at the injection site persisting for some time after the filler has been resorbed.[14]

Polycaprolactone is a new dermal filler, which also is a bioresorbable polymer that possesses collagen-stimulating properties.[15,16] It is a polymer of the aliphatic polyester family, and the degradation of polycaprolactone is slower than polylactic acid or polyglycolic acid, which are also aliphatic polyesters.[17,18] As a dermal filler, polycaprolactone is formulated as microspheres suspended in a gel carrier. This gel is an aseptic, latex-free, pyrogen-free, and complete bioabsorbable nonpermanent dermal filler.[15] Polycaprolactone gel has already been safely applied to fill NLFs, crow's feet, chin, and mandibular lines.[15] Previous studies have demonstrated that polycaprolactone-based treatment is a safe and effective way for NLF correction.[19–21] Recommendations for polycaprolactone-based dermal filler use for the face and hands have been published.[22]

Polycaprolactone has already been fully investigated in patients from many countries but not China. It is important because satisfaction might differ in different populations as there are aesthetic differences among populations.[23] Therefore, in this study, we explore the efficacy and safety of polycaprolactone gel in treating Chinese patients with moderate-to-severe NLFs.

Methods

Study Design and Patients

Eligible patients with moderate-to-severe NLF who wished to be treated by dermal fillers were recruited from three study centers between July 2017 and September 2019. This study was approved by the Ethics Committee of the hospitals who recruited patients in the study (Approval No. 2016BJYYEC-090-02). All patients participating in this study signed informed consent.

The inclusion criteria were (1) 18 to 75 years of age, (2) with severity scores of 3 or 4 for completely visible approximately symmetric bilateral NLF, and (3) wished to receive correction by intradermal injection described in this study protocol according to Wrinkle Severity Rating Score (WSRS). The major exclusion criteria were (1) hair, evident acne scars, active inflammation, infection, tumor, precancerous lesions, or unhealed wound in the NLF area that could interfere with the visual assessment of NLF severity and (2) the history of tissue transplantation or tissue filling by silica gel or other permanent or semipermanent dermal fillers.

Randomization and Blinding

The patients were randomized 1:1 into the two groups. Sealed envelopes were prepared according to a random number table before the initiation of the study. All the patients signed the informed consent and wore an eye patch, and the randomization envelope was opened and read by the third investigators (who were responsible for keeping the envelopes and preparing the syringes) according to the random number. The therapeutic investigators were responsible for the injecting polycaprolactone or sodium hyaluronate gel (as the control group) according to the randomization. Specifically, the patients in the study group were treated using the polycaprolactone gel (Ellanse TM-S; AQTIS Medical B.V.), and the patients in the control group were treated using the modified sodium hyaluronate gel (Restylane 2, Q-med AB). Blinding was applied for both investigators and patients in this study.

Procedure

The same procedures and equipment were used in the polycaprolactone group and the control group bilaterally. All patients received surface anesthesia. The filler was administered into the middeep dermis using a 27-G needle inserted at an approximate angle of 30 degrees parallel to the length of the fold. The patients were initially given a suboptimal dose, and the investigators were allowed to provide a touch-up at the 1-month follow-up visit. According to their willingness, the patients in the control group received a free compensatory injection of modified sodium hyaluronate gel (Restylane 2, Q-med AB) for bilateral NLF after unblinding and 1 year following the control injection.

Photos of the injection area were taken during follow-up to collect data for evaluating the WSRS of the patients, the same as other studies.[19,20] The photos were taken before the injection, on the day of injection, 2 weeks, 1 month, 3 months, 6 months, 9 months, and 12 months after injection respectively. The same photographer took the photos from the same angle and distance, and the area included the bilateral nasolabial areas. The photos were preserved for evaluation. The photos had to be symmetric from the view of originating sites of bilateral nasolabial areas, the chin tip, and the centerline of the lips. Photos were taken repeatedly to achieve an accurate assessment. The clearest photo was selected and preserved, while the other photos were archived.

Endpoints

The primary endpoint was the effectiveness rate at 12 months after injection by therapeutic investigator-reported. It was defined as the percentage of patients whose bilateral WSRS scores (the worse results of the bilateral sides were recorded for analysis) improved over $\geq$1 point during follow-up compared with the baseline.

The secondary endpoints were (1) the comparison of effectiveness rate between 6 months in the control group and 12 months after injection in the polycaprolactone group; (2) the comparison of the therapeutic investigator-reported WSRS changes among different time points of follow-up by 2 weeks,1 months, 3 months, 6 months, 9 months, and 12 months; (3) the comparison of the WSRS changes among different time points of follow-up by patient-reported; and (4) the comparison of the GAIS changes among different time points of follow-up by therapeutic investigator-reported.

The safety assessment included the responses of the treatment sites, signs, and symptoms assessed for 14 days after injection. In addition, the adverse events (AEs) were reported by therapeutic investigators and used for safety assessment. AE is defined as any adverse or unintended symptom, sign, or disease associated with the use of a study device over time, regardless of whether or not the device is associated. Severe adverse events (SAEs) are defined as AEs severe enough to cause loss of the ability to work and perform daily activities.

Sample Size Calculation

The patients were randomized 1:1 to the active and the control treatment group. In light of clinical data, it was assumed that the effective rate was 30% in the control group after treatment, and the effective rate in the polycaprolactone group could be at least 25% higher than that of the control group, of 55%. The α-value (two-sided) was set at 5%, and power was set at 80%. Considering a dropout rate of 20%, we planned to enroll 80 patients in each group, and 160 patients for the study.

Statistical Analysis

The full analysis set (FAS) included all patients who were randomized and treated in this study. The per-protocol set (PPS) included all patients who completed all the study procedures and did not have severe protocol deviations. The safety set (SS) included all patients randomized and who received the study treatment and with at least one safety assessment. The primary endpoint analysis was based on the FAS and PPS. All the baseline demographic data and secondary endpoints were analyzed based on the FAS. Safety analysis was performed based on the SS. Missing data were imputed using the last observation carry forward (LOCF) and the worst-case carry forward (WCCF) methods.

SAS 9.4 (SAS Institute, Cary, NY) was used for statistical analysis. Continuous data were reported as means $\pm$ standard deviations. Categorical data were reported as n (%). The paired *t*-test and repeated measures analysis of variance were used to compare the data before and after treatment. The *t*-test or Wilcoxon rank-sum test was used to analyze intergroup differences. All statistical analyses were two-sided. *p*-Values < 0.05 were considered statistically significant.

Results

Characteristics of the Patients

Of 160 patients enrolled, 80 patients were randomized in each group. ►**Fig. 1** presents the patient flowchart. The FAS and SS had 80 patients in each group, and the PPS had 77 and 78 patients in the polycaprolactone and control groups, respectively. They were middle-aged adults, mostly female and of Han ethnicity. According to the investigators, the left-side NFLs were moderate in 56.3 to 60.0% and severe in 40.0

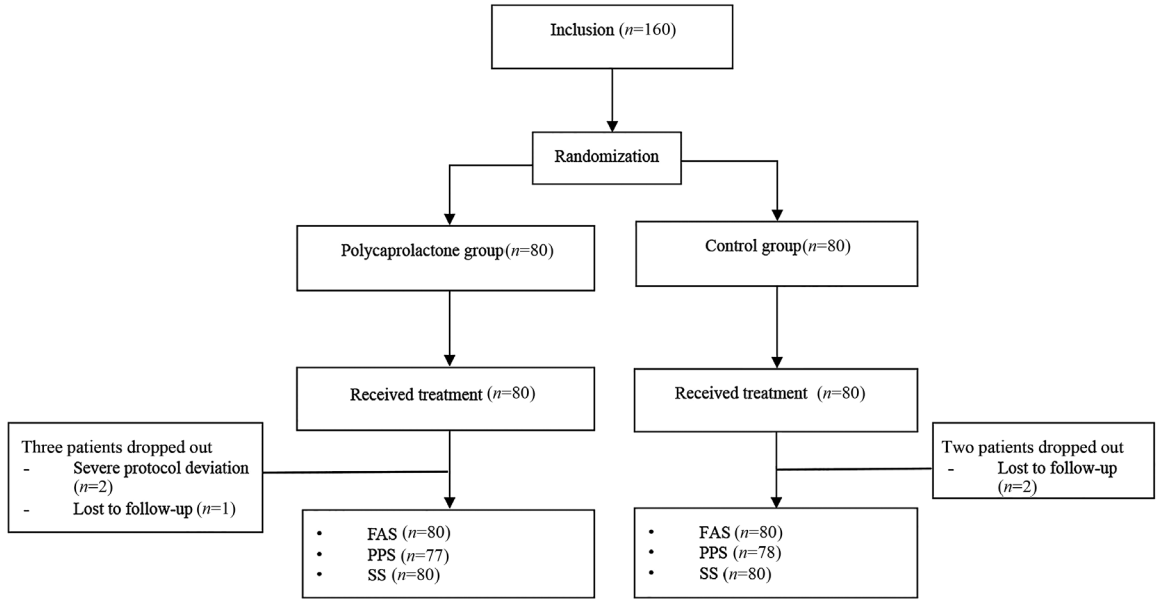

Fig. 1 Patient flowchart.

Table 1 Baseline characteristics (FAS)

Characteristic	Polycaprolactone $n=80$	Control $n=80$
Age (years), mean ± SD	42.9 ± 8.5	44.5 ± 8.7
Sex (female), *n* (%)	77 (96.3)	78 (97.5)
Ethnicity (Han), *n* (%)	77 (96.3)	74 (92.5)
Body weight (kg), mean ± SD	57.5 ± 7.8	57.2 ± 8.1
Height (cm), mean ± SD	162.5 ± 5.3	161.9 ± 5.5
BMI (kg/m^2), mean ± SD	21.8 ± 2.7	21.8 ± 2.7
Pregnancy check (negative), *n* (%)	66 (82.5)	61 (76.3)
NFL Assessment by investigators		
Left face, *n* (%)		
Moderate	48 (60.0)	45 (56.3)
Severe	32 (40.0)	35 (43.8)
Right face, *n* (%)		
Moderate	50 (62.5)	46 (57.5)
Severe	30 (37.5)	34 (42.5)
Assessment by patients		
Left face, *n* (%)		
Moderate	53 (66.3)	50 (62.5)
Severe	26 (32.5)	25 (31.3)
Right face, *n* (%)		
Moderate	53 (66.3)	51 (63.8)
Severe	24 (30.0)	25 (31.3)

Abbreviations: BMI, body mass index; FAS, full-analysis set; SD, standard deviations.

to 43.8% and the right-side NFLs were moderate in 57.5 to 62.5% and severe in 37.5 to 42.5% (►**Table 1**).

Primary Endpoints

As shown in ►**Table 2**, the investigator-reported effectiveness rate by 12 months in the polycaprolactone group was 88.8, 86.3, and 88.3% in the FAS (LOCF), FAS (WCCF), and PPS respectively, compared with 23.8, 22.5, and 23.1% in the control group respectively. The difference (95% CI) between the two groups was 28.7% (13.6%, 50.0%), 28.2% (12.7%, 50.6) and 29.8% (14.1, 52.3) respectively in the 3 analysis sets/methods. The difference between the 2 groups were very significant statistically at all the 3 analyses ($P<0.001$).

Secondary Endpoints

The effectiveness rate was 88.5% at 12 months in the polycaprolactone group, compared with 67.1% at 6 months in the control group ($p=0.001$; ►**Table 3**).

In the investigator-reported outcomes, as shown in ►**Fig. 2**, the improvement in WSRS remained relatively stable over 12 months in the polycaprolactone group, while the improvement in WSRS was gradually lost in the control group, starting at 3 months ($p<0.05$ at 3, 6, 9, and 12 months). As shown in ►**Fig. 3**, the GAIS assessment was improved, much improved, or very much improved in all patients during follow-up, while the proportion of patients with a "no change" assessment gradually increased during follow-up. Based on the patient-reported outcomes, the differences in the improvements in WSRS became significant between the two groups at 9 months (►**Fig. 4**). The patient-reported GAIS scores gradually declined with time in both groups but more severely in the control group (►**Fig. 5**).

Safety

The rates of AEs and SAEs were 45.0 versus 43.8% and 6.3 versus 3.8% in the polycaprolactone and control groups, respectively (►**Table 4**). The incidence of injection-related AEs and SAEs was 8.8 versus 11.3% and 0 versus 1.3% in the polycaprolactone and control groups, respectively. The most occurred injection-related AE was injection site swelling (22.2%) in the polycaprolactone group, and swelling (22.2%) and discoloration (22.2%) were the most occurred injection-related AEs in the control group (data not shown). All injection-related AE recovered, and no sequelae were observed. No patients dropped out due to the AEs or SAEs.

Discussion

To our knowledge, this was the first study that compared the efficacy and safety of polycaprolactone and sodium hyaluronate gel in treating Chinese patients with moderate-to-

Table 2 Comparison of effectiveness rate at 12 months after injection – Analyses with and without adjustment of center effects

Analysis Set	Before adjustment			After adjustment
	Polycaprolactone	Control	Difference (95%CI)	Difference (95%CI)
FAS[#]	71/80 (88.8%)	19/80 (23.8%)	28.7% (13.6; 50.0)	65.0% (53.4; 76.6)
FAS[*]	69/80 (86.3%)	18/80 (22.5%)	28.2% (12.7; 50.6)	63.8% (51.9; 75.6)
PPS	68/77 (88.3%)	18/78 (23.1%)	29.8% (14.1; 52.3)	65.2% (53.4:77.0)

Abbreviations: CI, confidence interval; FAS, full-analysis set; PP, per-protocol.
Note: *P*-value <0.0001 for comparisons between groups in all the analyses.
[#]Missing data imputed by LOCF (last observation carry over).
[*]Missing data imputed by WCCF (worst case carried-over).

Table 3 Effectiveness of polycaprolactone at 12 months versus the control group at 6 months

	Polycaprolactone	Control	*p*-Value
Effectiveness rate	69/78 (88.5%)	53/79 (67.1%)	0.0011

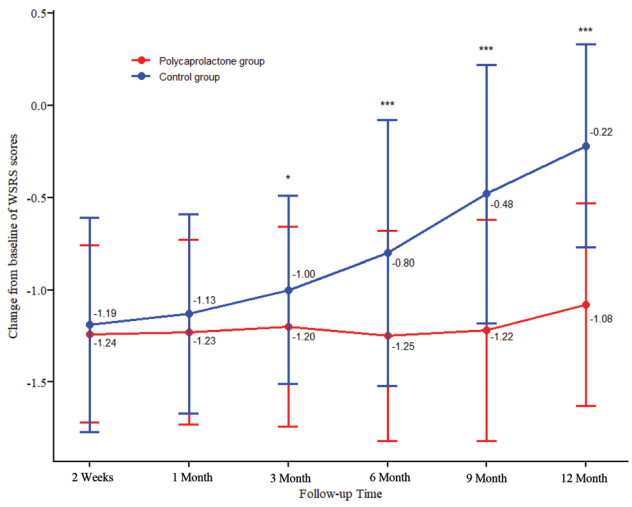

Fig. 2 Comparison of the wrinkle severity rating scale (WSRS) scores by investigator-reported during follow-up, $^{*}p < 0.05$, $^{***}p < 0.001$.

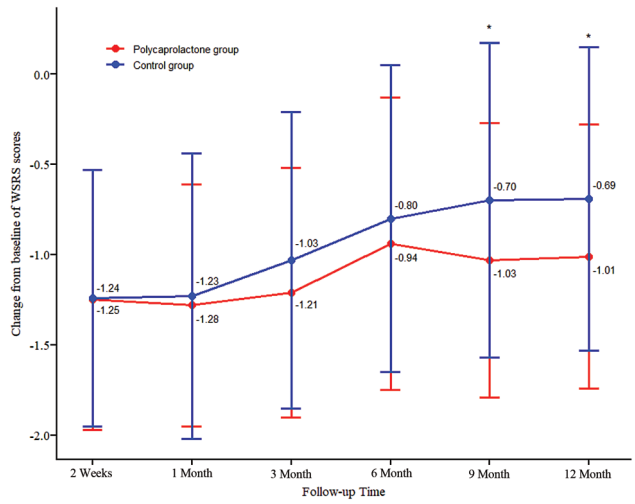

Fig. 4 Comparison of the wrinkle severity rating scale (WSRS) scores by patient-reported during follow-up, $^{*}p < 0.05$.

severe NLFs. In the FAS, the effectiveness rate at 12 months in the polycaprolactone group was 88.8% compared with 23.8% in the control. Furthermore, the improvement in WSRS remained relatively stable over 12 months in the polycaprolactone group, while the improvement in WSRS was gradually lost in the control group, starting at 3 months. No new safety signal was identified. The results suggest that polycaprolactone gel injection is effective and safe in moderate to severe NLFs in Chinese patients.

The WSRS and GAIS were used to assess the treatment efficacies of the fillers. In this trial, the effectiveness rate (based on a WRSR score improved by ≥1 point) was significantly higher in the polycaprolactone group than that in controls at 12 months, and the effectiveness rate at 12 months in the polycaprolactone group was higher than that in the control group at 6 months (−1.08 vs. −0.48). These results are supported by trials from Western populations.[19–21] In a split-face trial, the polycaprolactone-based dermal filler showed better WSRS scores at 6 (2.0 vs. 2.3), 9 (2.2 vs. 2.9), and 12 (2.6 vs. 3.1) months than a hyaluronic acid-based filler.[19] The results suggest the long-term stability of the volumize effect of polycaprolactone-based dermal filler. Indeed, the results suggested that the improvement in

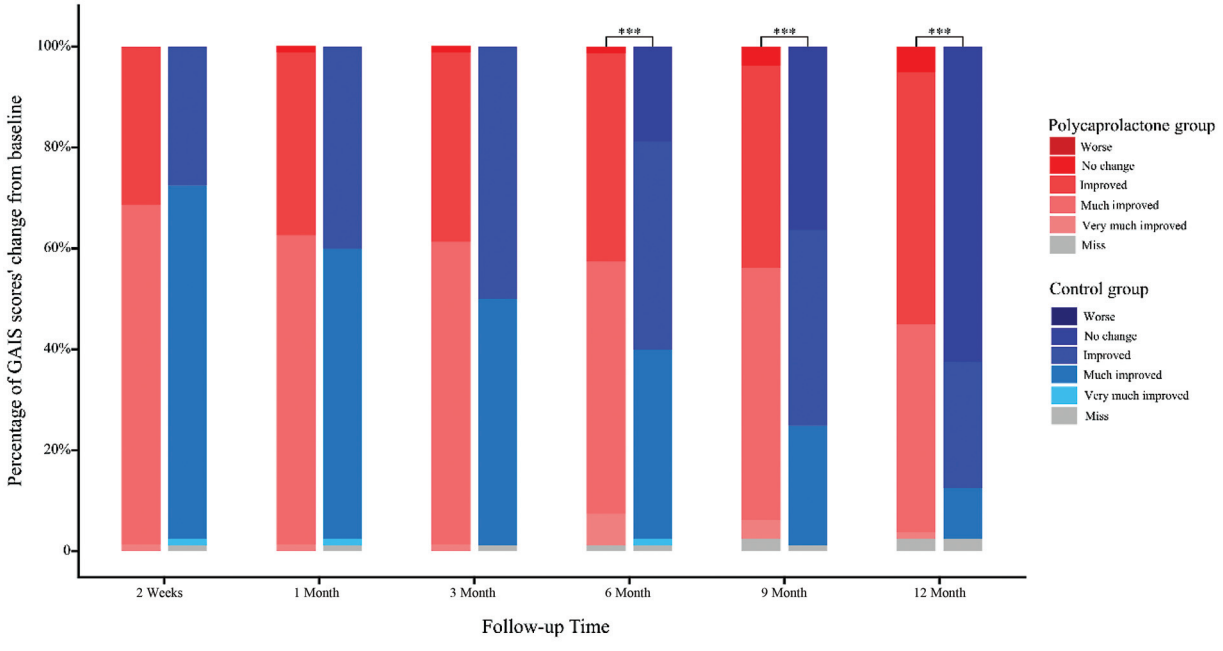

Fig. 3 Comparison of the global aesthetic improvement scale (GAIS) scores by investigator-reported during follow-up, $^{***}p < 0.001$.

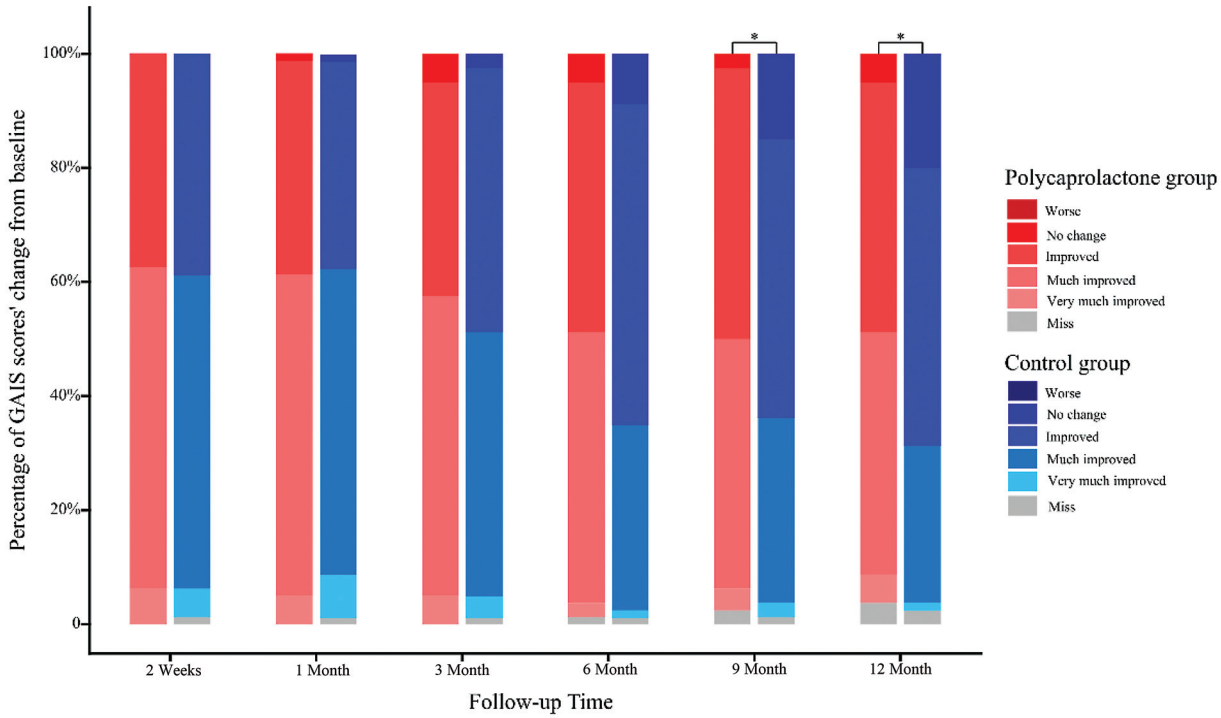

Fig. 5 Comparison of the global aesthetic improvement scale (GAIS) scores by patient-reported during follow-up, $^{*}p < 0.05$.

Table 4 Safety analysis

	Polycaprolactone ($n = 80$)	Control ($n = 80$)
Any AEs	36/80 (45.0%)	35/80 (43.8%)
SAEs	5/80 (6.3%)	3/80 (3.8%)
Injection-related AEs	7/80 (8.8%)	9/80 (11.3%)
Injection-related AEs	0/80 (0%)	1/80(1.3%)

Abbreviations: AEs, adverse events; SAE, serious adverse event.

WSRS was stable over the 12 months of follow-up, while the improvements in WSRS in the control group were gradually lost. It is also supported by European studies with follow-ups of 18 and 24 months; one showed an improvement of ≥1 point of WSRS in 92% at 6 months and 64% at 18 months,[21] while another study showed improvements of ≥1 point of WSRS at 24 months in at least 50% of patients who received two different formulations of polycaprolactone (Ellanse-S and Ellanse-M).[20]

In the present trial, the investigator's GAIS assessment showed improvements in nearly all patients of the polycaprolactone group over the 12-month follow-up, while the improvement rate decreased rapidly in the control group. In a split-face trial, the GAIS assessment showed that the total proportions of patients with improvements were higher at 6 (85 vs. 64%), 9 (41 vs. 0%), and 12 (20 vs. 0%) months in the polycaprolactone group compared with a hyaluronic acid-based filler.[19] At 12 months, the improvement rate on GAIS showed improvements in 90 and 91.4% of patients who received Ellanse-S and Ellanse-M, respectively,[20] which were similar in the present trial (>90% in the polycaprolactone group). Moers-Carpi and Sherwood reported an investigator-evaluated GAIS improvement rate at 24 months of 77.8 and 100% using Ellanse-S and Ellanse-M, respectively.[20] Another multicenter clinical study by Moers-Carpi et al[21] that included 90 patients with moderate-to-severe NLFs followed for 18 months after a single injection and no touch-up showed that significant improvement of GAIS was observed similarly by the physicians and the subjects in more than 90% of subjects up to 12 months and 81% of subjects at 18 months.

Therefore, the long-term efficacy based on the WSRS and GAIS observed in Chinese patients appears to be similar to the long-term efficacy observed in Western patients. Future studies will be conducted to determine the long-term effect of polycaprolactone-based dermal filler in Chinese. Still, a study in Koreans showed that the GAIS was maintained for 24 months in patients who underwent forehead augmentation using a polycaprolactone-based gel.[24]

Compared with other studies,[15,19–21] no new safety signals were found. A study of 1,111 patients performed in France and Taiwan showed that the complication rate of polycaprolactone-based gel was low, with edema lasting >2 weeks observed in 4.5% of the 1111 patients, bruising in 2.7%, malar edema in 0.7%, temporary lump in 0.5%, and discoloration in 0.2%; in addition, no nodules or granuloma were observed over 3 years of follow-up.[25] In the present study, the AEs were all responses at the injection site, such as swelling and reddening, which all disappeared without sequelae.

This trial has limitations. The follow-up was relatively short. More studies are needed to investigate the long-term effects further. More safety data should be collected in the future.

In conclusion, polycaprolactone gel injection is effective and safe to treat moderate-to-severe NLFs in Chinese patients. Furthermore, this trial confirms the outcomes of the polycaprolactone dermal filler in Chinese patients.

Author Contributions
H.Z., Q.S., and Y.T. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. H.Z. was involved in the study concepts and design. All authors (H.Z., R.R., S.B., W.Q., X.M, R. W., X.L., R.F., Q.S., and Y.T.) involved in the acquisition, analysis, and interpretation of data. C.Z. involved in data collection, J. S. and H. Z. involved in the draft of the manuscript.

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Conflict of Interests
None declared.

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