ORIGINAL ARTICLE

Cosmetic

A Randomized, Active-Controlled, 52-Week Study of Hyaluronic Acid Fillers for Anteromedial Malar Region Augmentation

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Background: Hyaluronic acid (HA) fillers for volume augmentation in the anteromedial malar region of Asians have been popular for many years. However, studies on their long-term effectiveness are lacking. This study aimed to evaluate the effectiveness and safety of HA fillers injected into the anteromedial malar region for volume augmentation for up to 52 weeks.

Methods: Each anteromedial malar region of the subjects was treated with YVOIRE Contour (YVO_C) in one side and Restylane Sub-Q (RES_S) in the other and followed up at weeks 2, 14, 26, and 52. The volume using the mid-face aesthetic scale (MFAS) ranging from 0 (full) to 4 (very severely sunken) and the subject's satisfaction and adverse events were evaluated.

Results: Total 83 subjects were randomized and treated with YVO_C and RES_S. The LS means (standard error) of MFAS score in the YVO_C and RES_S groups were both 2.56 (0.05) at baseline, 1.32 (0.07) and 1.39 (0.07) at week 26, and 1.84 (0.10) and 1.89 (0.10) at week 52, respectively. The difference in the LS mean of MFAS score between the groups at week 26 was 0.07 (95% confidence interval, 0.01–0.12), showing the non-inferiority of YVO_C to RES_S. About 70% of subjects were still satisfied with the results at week 52. No specific safety concern was detected.

Conclusions: The HA fillers injected for the anteromedial malar augmentation maintained the volume well for up to 52 weeks. Additionally, both YVO_C and RES_S show similar effectiveness and safety profiles. *(Plast Reconstr Surg Glob Open 2020;8:e2648; doi: 10.1097/GOX.0000000000002648; Published online 26 February 2020.)*

INTRODUCTION

Decreased skin elasticity and thickness, the loss of soft tissue volume and bony mass, and redistribution of fat tissue all contribute to the formation of wrinkles and folds, which are characterized as the signs of aging.[1] These also change the facial contour, especially around the mid-face due to volume loss.

To make patients look younger, several surgical procedures have been performed in the past, and many surgeons are in search for safer and more effective treatments in these fields. Particularly, hyaluronic acid (HA)-based fillers have been widely used recently not only for the correction of facial lines and folds but also for contour and volume augmentation because of their safety and effectiveness.[1–3] Moreover, it can be easily removed with hyaluronidase. Thus, it is used most popularly in fillers.[3,4]

For the mid-facial volume restoration, various HA fillers including YVOIRE Contour (YVO_C; LG Chem, Ltd., Seoul, Republic of Korea) and Restylane Sub-Q (RES_S; Q-Med AB, Uppsala, Sweden) are used in many countries. Although Juvederm Voluma (Allergan Inc., Irvine, CA, USA) has been approved firstly for the volume

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augmentation in the mid-face in 2013 by the US Food and Drug Administration, studies on HA fillers administered for the mid-face augmentation are very limited, and most studies were conducted in Caucasians. However, Asians who have wider, shorter, and flatter faces[5] with a different concept of standard beauty from Caucasians[6,7] prefer round apple cheeks without zygomatic region in the mid-face.[5] Therefore, mid-face filler injection in Asians is made mostly for the restoration of the anterior projection, targeting the medial aspect of the zygoma and submalar regions.[5] However, studies on the effectiveness of HA fillers on Asian mid-face augmentation are lacking.

Thus, this study aimed to evaluate long-term effectiveness and safety of two HA fillers, YVO_C and RES_S, both of which are used widely in the Republic of Korea and injected into the anteromedial malar region of Koreans.

METHODS

Study Design

The study was a multicenter, randomized, active-controlled, split-face design, rater-blind, comparative clinical study conducted in 2 teaching hospitals in the Republic of Korea from June 2014 to October 2015. With split-face of each subject, YVO_C or RES_S was assigned and injected randomly into the right or left anteromedial malar region by the investigators via the random assignment table generated by a statistician. Then, they were followed up at weeks 2, 14, 26, and 52 after HA filler injection.

The study was conducted in compliance with the ethical guidelines of the Declaration of Helsinki and Good Clinical Practices and was approved by the institutional review board of each study site. Written informed consent was obtained from each participant, and this study was registered at ClinicalTrials.gov, NCT02119780.

Subject Selection and Treatment

The study included male or female adults aged between 20 and 65 years. Only the subjects who had more than moderate volume loss [ie, score 2–4, rated using the 5-point photograph numeric mid-face aesthetic scale (MFAS); "Upper Cheek Fullness—At Rest"[8] (Table 1)] in both anteromedial malar regions symmetrically were included. Major exclusion criteria included subjects with active or infectious skin diseases, uncured wounds or tumors on the mid-face area, subjects with history of radiotherapy in the mid-face area, subjects with history of laser therapy, chemical peeling or dermabrasion in the mid-face area within 3 months before randomization, and subjects who received fillers or botulinum toxin treatment or facial surgery within 12 months before randomization.

YVO_C is a biphasic HA filler crosslinked with 1,4-Butanediol diglycidyl ether with a HA content of 22 mg/mL. The median particle size (DV50) of YVO_C is around 1,200 μm (range 1,000 to 1,500 μm). RES_S is also a biphasic HA filler crosslinked with 1,4-Butanediol diglycidyl ether (20 mg/mL of HA) and consists of large particles. The remarkable feature of YVO_C unlike RES_S is that it consists of large particles mixed with small particles to fill voids between large particles.

Table 1. MFAS and Upper Cheek Fullness—At Rest

Score	Degrees of Severity
0	Full upper cheek
1	Mildly sunken upper cheek
2	Moderately sunken upper cheek
3	Severely sunken upper cheek
4	Very severely sunken upper cheek

According to the random assignment table, YVO_C and RES_S were injected into the subcutaneous layer of the assigned side of the anteromedial malar region using a 21-gauge cannula by the same treating investigator. If necessary, a local anesthetic was used equally on both anteromedial malar regions at the discretion of the treating investigator. HA fillers were injected to achieve optimal correction for each subject, and one touch-up treatment was allowed after 2 weeks of the initial injection. The maximum acceptable volume was 4.0 mL for one side of the anteromedial malar region for each treatment.

Assessments

The effectiveness of volume restoration was evaluated using MFAS and Global Aesthetic Improvement Scale (GAIS[9]; Table 2). MFAS, a 5-point photograph numeric validated grading scale[8] developed by Merz Pharma GmbH, was used after the written copyright licensing agreement was made between the sponsor (LG Chem, Ltd.) and Merz Pharma GmbH. In this study, "the Upper Cheek Fullness—At Rest" was used (Table 1). Three qualified independent blinded raters who were trained in the MFAS evaluation in advance evaluated the volume of the anteromedial malar region. GAIS, a measure of the relative overall improvement after HA filler injection compared to the pre-injection, was evaluated by the subjects (Table 2).

The primary parameter was the mean MFAS score at week 26 after HA filler injection. The secondary parameters included the mean MFAS score at weeks 2, 14, and 52 after HA filler injection, changes in mean MFAS score from baseline at each evaluation time point, percentage of the subjects with improvement in MFAS score by at least 1 grade from baseline (MFAS responder rate), mean GAIS score, and percentage of the subjects with improvement in GAIS score by at least 1 grade from baseline (GAIS responder rate).

Adverse events (AEs) were collected at each visit for safety evaluation. Solicited local AEs (pain, tenderness, swelling, redness, bruising, itching, papule, and pigmentation) occurring at the injection site were evaluated for 14 days after HA filler injection through the subject diary.

Statistical Analyses

The sample size to demonstrate the non-inferiority of YVO_C compared to RES_S with regard to the mean MFAS score at week 26 was calculated with a 90% power at the significance level of 2.5% and a one-sided test. The planned enrollment was 83 subjects, assuming a drop-out rate of 20%.

Table 2. The Global Aesthetic Improvement Scale

Score	Rating	Description
3	Very much improved	Optimal cosmetic result for the implant in this patient
2	Much improved	Marked improvement in appearance from the initial condition, but not completely optimal for this patient. A touch-up would slightly improve the result
1	Improved	Obvious improvement in appearance from the initial condition, but a touch-up or retreatment is indicated
0	No change	The appearance is essentially the same as the original condition
−1	Worse	The appearance is worse than the original condition

Statistical analysis was performed using SAS version 9.3 (SAS Institute, Cary, NC, USA). All effectiveness parameters are based on the descriptive statistics. Wilcoxon's signed rank test was performed to test for the changes in mean MFAS score in each treatment group from baseline at each evaluation time point including primary time point of week 26. The 2-sided 95% confidence interval (CI) for the difference in mean MFAS score between treatment groups was estimated in the mixed-effects model considering a split-face design, and the non-inferiority of the YVO_C in terms of effectiveness at week 26 can be demonstrated if the lower limit of the 95% CI was greater than −0.32. For the responder rates, the 2-sided 95% CI for the difference in rates between treatment groups was summarized. Safety data were presented in descriptive statistics.

RESULTS

Subject Characteristics

A total of 87 subjects were screened, 83 subjects were enrolled, and 68 subjects completed the study up to week 52 (Fig. 1). Fifteen subjects were excluded from the study
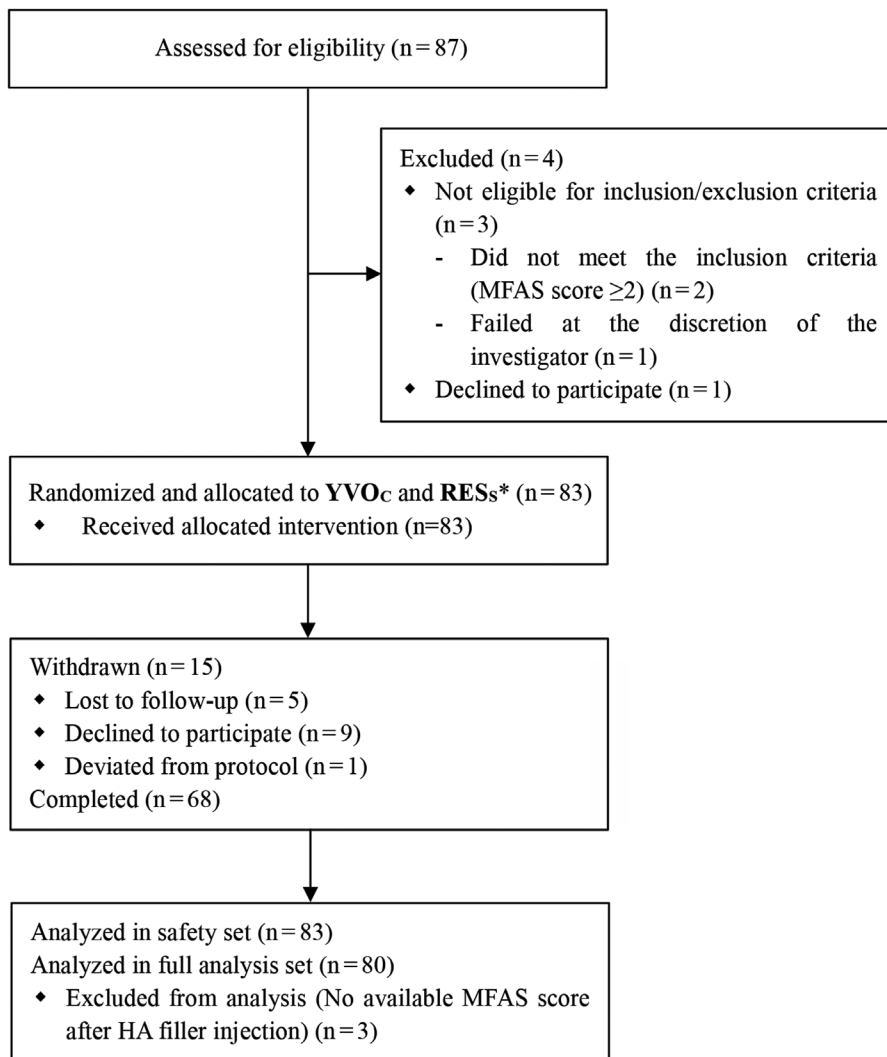

Fig. 1. Subject dispositions. *Subjects were randomly assigned to which side of the facial antero-medial malar region they would be injected with either YVO_C or RES_S.

Table 3. HA Injection Volume (Safety Set)

	YVO_C	RES_S
Injection volume in subjects who did not receive touch-up treatment (mL)		
N	75	66
Mean (SD)	1.60 (0.41)	1.51 (0.36)
Min, max	0.80, 2.80	0.80, 2.60
Total injection volume in subjects who received touch-up treatment (mL)		
N	8	17
Mean (SD)	2.14 (0.22)	2.17 (0.52)
Min, max	1.80, 2.50	1.40, 3.50
Total injection volume in total subjects (mL)		
N	83	83
Mean (SD)	1.65 (0.42)	1.65 (0.47)
Min, max	0.80, 2.80	0.80, 3.50

Max, maximum; Min, minimum.

Table 4. Mean MFAS Score over Time Evaluated by the Independent Blinded Raters (Full Analysis Set)

	YVO_C (N = 80)	RES_S (N = 80)	LS mean difference (95% CI)
Baseline	2.56 (0.05)	2.56 (0.05)	0.00 (−0.04 to 0.04)
Week 2	0.85 (0.07)	0.90 (0.07)	0.05 (0.00 to 0.10)
Week 14	1.02 (0.08)	1.09 (0.08)	0.06 (0.01 to 0.12)
Week 26	1.32 (0.07)	1.39 (0.07)	0.07 (0.01 to 0.12)
Week 52	1.84 (0.10)	1.89 (0.10)	0.05 (−0.02 to 0.13)

Data are presented as LS mean (SE) unless otherwise indicated; data were analyzed using a mixed effects model including treatment and week as repeated measures effects and the subject as random effect; LS mean difference was calculated as RES_S group—YVO_C group.

before week 52 due to follow-up loss (n = 5), withdrawal of consent (n = 9), and deviation from the study protocol (n = 1). The mean age of the subjects who participated in this study was 44 (24–63) years, and 91% of the subjects were female participants. All the randomized subjects were treated with YVO_C and RES_S in the same way, using the linear threading and fanning technique for both anteromedial malar regions. Table 3 shows a summary of the total HA injection volume.

Clinical Results

The least squares (LS) mean [standard error (SE)] of MFAS score at baseline was 2.56 (0.05) in both groups. The LS mean (SE) of MFAS score at week 26 was 1.32 (0.07) in the YVO_C group and 1.39 (0.07) in the RES_S group, and the LS mean change (SE) from baseline was −1.23 (0.06) and −1.16 (0.06) in the YVO_C and RES_S groups, respectively. The LS mean changes in MFAS score at week 26 were significant in both groups compared with the baseline (P-value <0.0001). In addition, the difference in the LS mean of MFAS score between the groups at week 26 was 0.07 (95% CI, 0.01–0.12), and since the lower limit of the 95% CI of the difference was greater than −0.32, the non-inferiority of YVO_C to RES_S was demonstrated. The

analysis of covariance adjusted for total injection volume was also performed, and the LS means of MFAS score at week 26 were comparable between the groups [**see table, Supplemental Digital Content 1**, which displays analysis of covariance on the change from baseline at week 26 of MFAS score evaluated by the independent blinded raters (full analysis set), *http://links.lww.com/PRSGO/B311*].

The LS mean of MFAS score from baseline up to week 52 after HA filler injection is presented in Figure 2 and Table 4. The LS mean (SE) of MFAS score at week 52 was 1.84 (0.10) and 1.89 (0.10), and the LS mean change (SE) from baseline was −0.73 (0.08) and −0.68 (0.08) in the YVO_C and RES_S groups, respectively (Fig. 3). The LS mean changes in MFAS score at week 52 were significant in both groups compared with the baseline (P-value <0.0001). In addition, the effectiveness of volume restoration was similar between the groups during the 52-week follow-up period.

In both of the groups, all the subjects showed at least 1 grade improvement in MFAS score up to week 14 after HA filler injection (Fig. 4A). At week 26, the MFAS responder rates were 95% and 93% in the YVO_C and RES_S groups, respectively. At week 52, the rates were 66% and 61%, respectively.

The GAIS responder rates (improvement by at least 1 grade compared to pre-treatment) were 78% and 79% in the YVO_C and RES_S groups at week 26 and 69% and 72% at week 52, respectively (Fig. 4B). Moreover, no significant
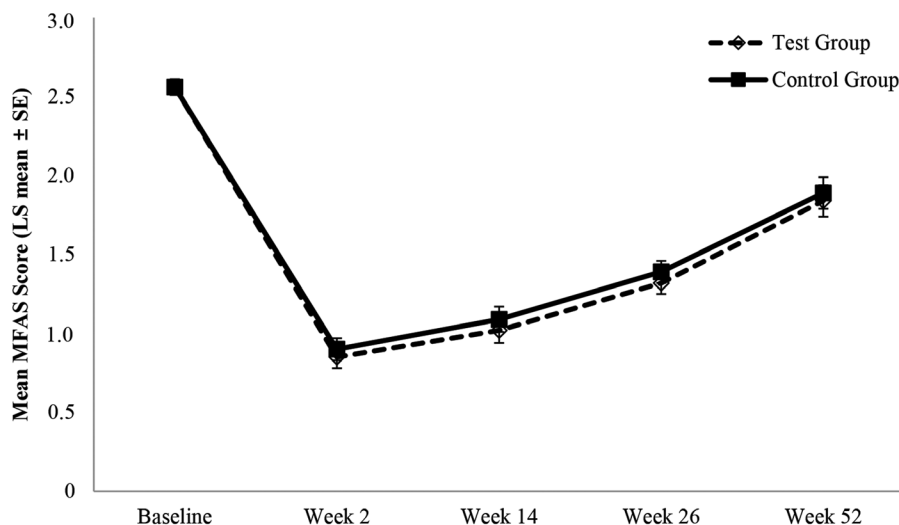

Fig. 2. Mean MFAS score over time evaluated by the independent blinded raters (full analysis set).
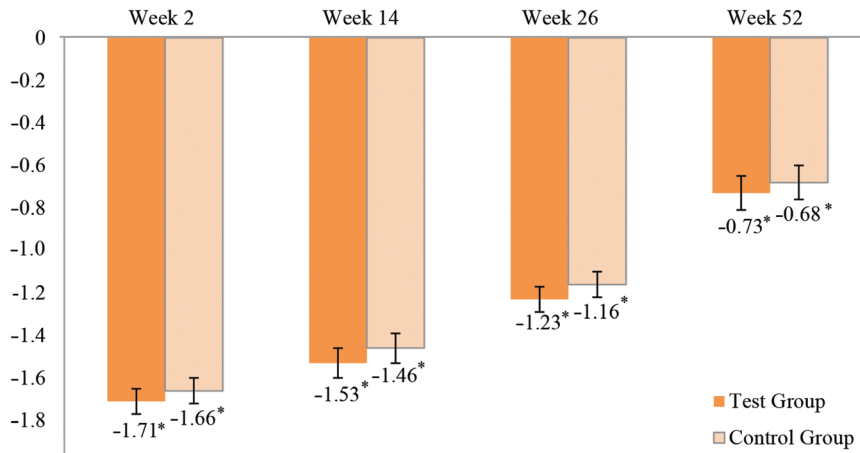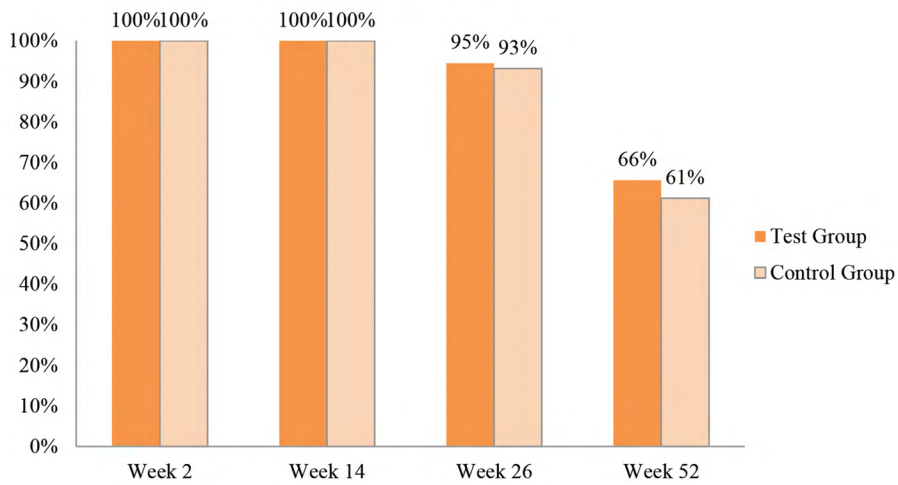
The Mean Change from Baseline in MFAS Score

Fig. 3. The mean change from baseline in MFAS score evaluated by the independent blinded raters (full analysis set). Data are the LS mean ± SE. *P-value <0.05, P-value was obtained from Wilcoxon's signed rank test.

MFAS Responder Rate
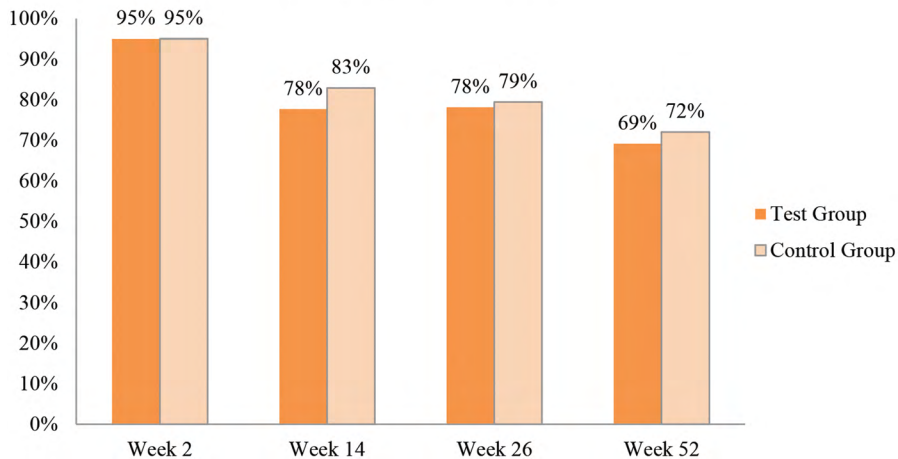

GAIS Responder Rate

Fig. 4. A, MFAS responder rate evaluated by the independent blinded raters (full analysis set); (B) GAIS responder rate evaluated by the subjects (full analysis set).
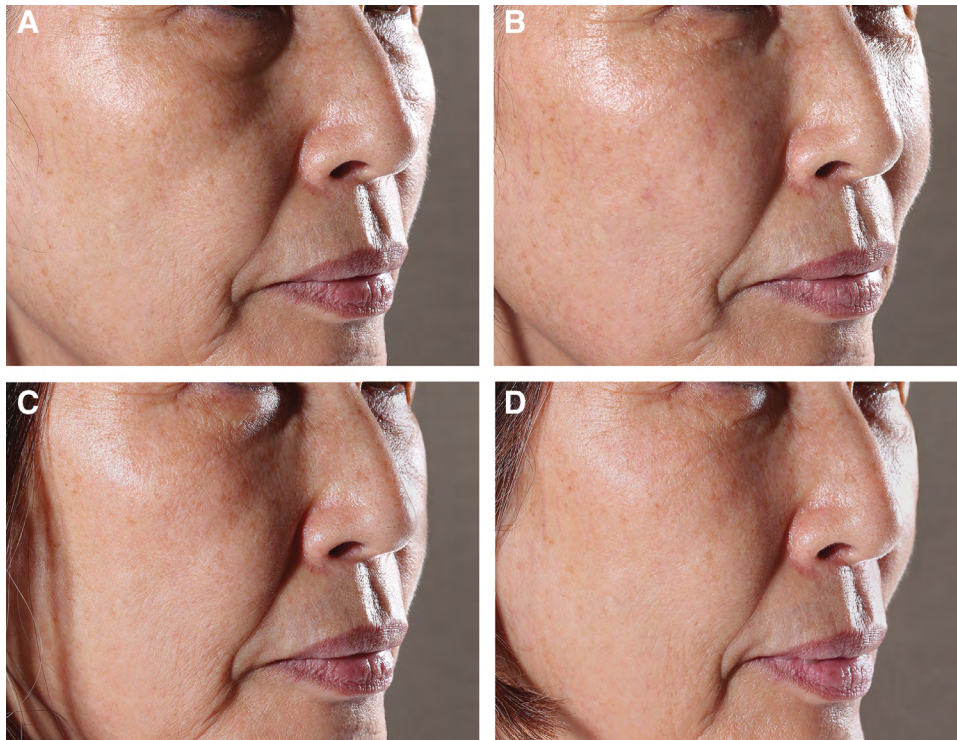
Fig. 5. Photographs of a representative subject (A) before treatment, (B) 2 weeks after (optimal state), (C) 26 weeks after, and (D) 52 weeks after HA filler injection into the anteromedial malar region.

difference was observed between the groups at all time points of measurement. Figure 5 shows a pre- and posttreatment photograph of a representative subject.

The incidence rates of solicited local AEs were in a range of 36%–93%, showing a similar level between the groups (Table 5). All the solicited local AEs were recovered within 14 days after HA filler injection. In addition, the subgroup analysis, divided by the median of the total injection volume in each treatment group, showed that the incidence and duration of solicited local AEs were similar in the low and large volume subgroups [**see table, Supplemental Digital Content 2**, which displays solicited local AEs by total injection volume after initial injections (safety set), *http://links.lww.com/PSYMED/A601*].

The most frequently reported AEs were gastroenteritis (3.6%) and upper respiratory tract infection (3.6%), which were not related to HA filler injection. Interestingly, delayed-onset swelling of the face was observed in one case. This subject experienced the immediate solicited local AEs including pain, tenderness, swelling, redness, and pigmentation, which recovered completely within 4 days after HA filler injection. However, mild swelling was observed in the RES_S injected side at day 31 and also in the YVO_C injected side at day 62. This fully recovered within 5 days with administration of steroids and antibiotics.

DISCUSSION

To the best of our knowledge, this was the first clinical study of follow-up for a long-term of 1 year after HA filler injection for the anteromedial malar volume restoration in the mid-face in Korean subjects. In this study, YVO_C and RES_S were injected into the anteromedial malar region in each side of the mid-face to evaluate the effectiveness and safety of HA fillers injected for volume augmentation. Since both products are large particle-stabilized HA-based fillers, which are most similar in particle form as composed through a biphasic cross-linking procedure of HA and also similar in overall composition and physicochemical properties, they were suitable for assessing the long-term effectiveness and safety of HA fillers and also comparison of the differences in HA fillers.

This study was conducted as a split-face design in which YVO_C and RES_S were injected into the anteromedial malar region in each side of a subject, and thus, each subject functioned as the test group as well as the control group,

Table 5. Solicited Local AEs after Initial Injections (Safety Set)

	YVO_C (N = 83)	RES_S (N = 83)
Any solicited AEs, n (%)	82 (98.80)	83 (100.00)
Pain, n (%)	77 (92.77)	74 (89.16)
Tenderness, n (%)	77 (92.77)	81 (97.59)
Swelling, n (%)	65 (78.31)	68 (81.93)
Redness, n (%)	49 (59.04)	52 (62.65)
Bruising, n (%)	30 (36.14)	28 (33.73)
Itching, n (%)	27 (32.53)	31 (37.35)
Papule, n (%)	31 (37.35)	31 (37.35)
Pigmentation, n (%)	30 (36.14)	30 (36.14)
Duration, days		
Pain, mean (SD)	3.70 (4.29)	3.84 (4.13)
Tenderness, mean (SD)	8.57 (9.83)	6.85 (5.71)
Swelling, mean (SD)	12.71 (16.10)	10.54 (14.20)
Redness, mean (SD)	4.06 (4.03)	4.13 (3.78)
Bruising, mean (SD)	9.03 (10.62)	5.25 (3.95)
Itching, mean (SD)	4.89 (5.50)	4.87 (5.40)
Papule, mean (SD)	10.48 (15.74)	9.61 (11.68)
Pigmentation, mean (SD)	6.67 (9.75)	6.17 (6.43)

minimizing the difference in characteristics of subjects between the groups. In addition, to eliminate the bias by the treating investigator in the effectiveness evaluation, the MFAS scores evaluated by 3 independent blinded raters were used, and the subjects evaluating the GAIS were also kept blinded.

In the evaluation of MFAS scores, the volume augmentation was in optimal state at week 2 after HA filler injection. Then, the LS means of MFAS score increased gradually up to week 52. At week 52, the LS mean of MFAS score was still lower than those at baseline in both groups, showing the sustained effectiveness of volume augmentation in the anteromedial malar region up to week 52 after HA filler injection. Moreover, at week 52, MFAS responder rates were 66% and 61% in the YVO_C and RES_S groups, respectively.

Not only the results of the primary effectiveness endpoint, but the results of the other endpoints, including the mean MFAS score and the mean GAIS score at each evaluation time point, show similar trends between the YVO_C and RES_S groups. As RES_S has already been established for its effectiveness through many studies,[10–15] the effectiveness and safety of YVO_C in anteromedial malar volume restoration of Asian could be confirmed through this study.

Compared with Caucasians' data[16] regarding the improvement rate of 83.2% at month 6 after HA filler injection, the responder rates of this study were higher up to 95% and 93%. Considering the differences in facial structure and optimal correction for each subject between Caucasians and Asians, a little more injected HA volume in this study, and the difference in volume evaluation scales might have resulted in the difference in the responder rates.

As mentioned before, a delayed-onset swelling was reported as shown in the other reports.[17–22] The exact causes of this phenomenon have not been identified; it is proposed that it may be due to infection during injection, larger boluses or higher volumes, injection technique and placement, immune system activation of the subject, residual bacterial and/or avian proteins from the HA production process, impurities, or remnants of the chemical agents used in the cross-linking (stabilizing) process.[17–22] In this case of the present study, we did not conduct pathologic examination or MRI imaging, because the symptom was mild and the subject did not want to undergo any other procedures. Although the cause of this reaction was not found, it fully recovered within 5 days after administration of steroids and antibiotics, and the causal relationship with HA filler injection was evaluated as unlikely.

In the present study, the subjects were followed up for 1 year after HA filler injection, but the number of subjects who could be evaluated at week 52 was reduced to 68. This may be considered a limitation. Most subjects were withdrawn due to withdrawal of consent or follow-up loss during the follow-up period, suggesting that the subjects dropped out of the study because of the prohibition of additional aesthetic treatments such as other fillers or botulinum toxin treatment on the face during the follow-up period. However, this was inevitable for evaluating the long-term effectiveness and safety of injected HA fillers. In addition, the drop-out rate was assumed to be 20%, but the actual drop-out rate was lower than this, and there was no effect on the effectiveness evaluation.

As an extension of this study, long-term follow-up for up to 2 years after HA filler injection was conducted, and the results will be addressed later.

CONCLUSIONS

It was confirmed that the HA fillers injected in the anteromedial malar region for volume augmentation of Asians are quite effective at week 26 and the volume was well maintained up to week 52. It was also proved that YVO_C shows similar effectiveness and safety profiles as RES_S.

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