



Split-Face Comparison of Two Hyaluronic Acid Fillers: Intersection of Rheology and Tissue Behavior in Midface Rejuvenation

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Abstract

Background: Hyaluronic acid (HA) fillers are one of the most popular aesthetic treatments for midface volumization, achieving optimal aesthetic improvements. Given the variety of HA filler products available, it is important for injectors to understand how their rheological properties can influence behavior in tissues.

Objectives: To evaluate and compare (1) product integration and dynamic support and (2) lifting capacity of 2 rheologically different HA fillers (HA Contour [HA_{CON}] and HA Voluma [HA_{JVOL}]) through ultrasound and clinical photography.

Methods: Randomized, split-face study ($n = 11$) comparing 2 midface HA fillers over a 12-month period with initial injection along the zygomatic arch at Day 0 and optional touch-up at Month 1. Eligible patients were aged 22 to 65 years with midface volume loss and contour deficiency. Assessments included ultrasound (neutral and smiling), clinical photography with 3D volume change (lifting capacity) analyses, and adverse event reporting. Volume change was assessed at 2 regions: midface and infraorbital hollow (IOH).

Results: With similar average total injection volumes, both fillers had comparable lifting capacity in the midface (HA_{CON}: ≥ 2.07 mL and HA_{JVOL}: ≥ 2.08 mL; $P > .05$) and IOH (HA_{CON}: ≥ 0.45 mL and HA_{JVOL}: ≥ 0.57 mL; $P > .05$) areas for up to 12 months. Ultrasound showed that HA_{CON} integrated into the tissue, stretching and elongating during a smiling expression, whereas HA_{JVOL} did not integrate as much, with aggregates consistent in size and shape during both neutral and smiling expressions through 12 months. No adverse events were reported during the study.

Conclusions: HA_{CON} demonstrated a similar duration of lifting capacity (volumization) as HA_{JVOL} but had more distributed product integration and flexibility to support dynamic expressions through 12 months.

Level of Evidence: 3 (Therapeutic)

Aging in the midface is characterized by decreased skin elasticity and thickness, loss of tissue volume and mass, and redistribution of fat pads, resulting in wrinkles, folds, and sagging.¹ More recently, cosmetic treatment of midface aging has emphasized replacing volume loss and improving contouring. Injectable hyaluronic acid (HA) fillers are one of the most popular noninvasive aesthetic treatments for midface volume restoration because of their safety profile, proven efficacy, and reversibility.¹ In addition to a desirable brief recovery time, patients want natural-looking results from HA fillers, which are subjected to a variety of stresses and deformations after injection, including mechanical deformations resulting from muscle and tissue movements.² Natural-looking results are achieved when HA fillers are able to support dynamic facial movements.³ Indeed, a natural-looking appearance of the whole face in motion is a key attribute desired by

patients since facial movements facilitate the ability of other people to understand emotions.

There are a variety of HA filler variants available for injection that have differing characteristics and clinical effects.⁴ Two well-known fillers FDA-approved for midface volumization are Restylane Contour (HA_{CON}; Galderma, Uppsala, Sweden) and Juvéderm Voluma (HA_{JVOL};

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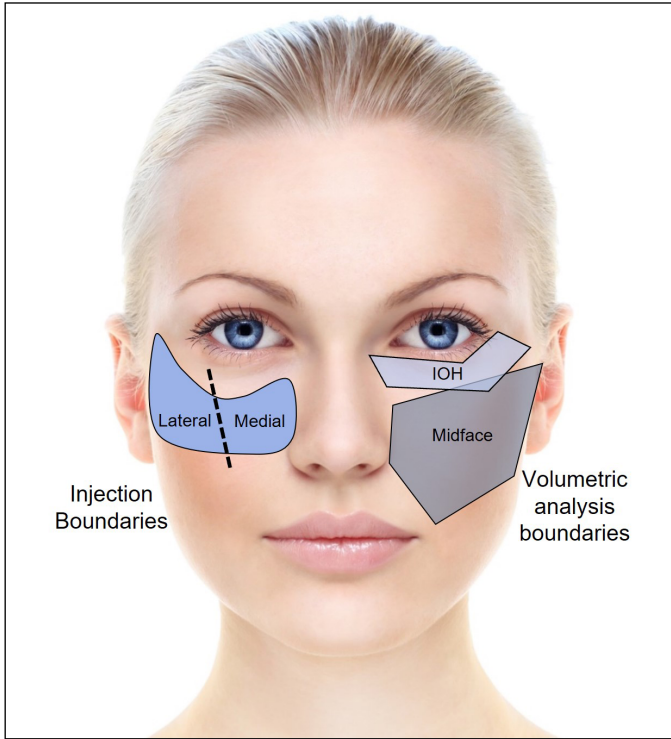


Figure 1. Area boundaries for injection (left) along the medial and lateral zygomatic arch and volumetric imaging analysis (right) for midface and infraorbital hollows (IOHs). Note that injections were not performed in the IOH area. Image courtesy of Valentina Razumova/Shutterstock.

Table 2. Treatment Volume

| | | | HA _{CON} (mL) | HA _{JVOL} (mL) |
|--|----------------|----------|------------------------|-------------------------|
| Initial (Day 0) <i>n</i> = 11 | Total amount | Average | 1.5 | 1.6 |
| | | Min, max | 0.7, 2.4 | 1, 2.5 |
| Touch-up (1 month) ^a | Total amount | Average | 0.4 | 0.4 |
| | | Min, max | 0, 0.8 | 0, 1.4 |
| Initial + touch-up (<i>n</i> = 10) ^b | Total amount | Average | 1.9 | 1.9 |
| | | Min, max | 0.7, 3.2 | 1.0, 3.4 |
| | Medial amount | Average | 1.5 | 1.5 |
| | | Min, max | 0.5, 2.7 | 0.7, 3.4 |
| | Lateral amount | Average | 0.4 | 0.4 |
| | | Min, max | 0, 0.8 | 0, 0.8 |

HA, hyaluronic acid. ^aTwo out of 11 received HA_{CON} touch-up only; 1 out of 11 received HA_{JVOL} touch-up only; 3 out of 11 did not receive touch-up. ^bOne patient was removed from the average initial + touch-up volume and thus from 6-, 9-, and 12-month analyses because of protocol violation.

Allergan Aesthetics, Irvine, CA). They each contain 20 mg/mL of HA with different crosslinking gel technologies that result in the distinct rheological properties.² HA gels with high strength/firmness, measured as *G* prime (*G'*), are stronger and more resistant to deformation (typical range,

Table 1. Baseline Demographics (*n* = 11)

| Patient numbers | <i>n</i> | % |
|------------------------|------------|------|
| Age | | |
| Mean, years (range) | 46 (32-61) | |
| Gender | | |
| Female | 9 | 81.8 |
| Male | 2 | 18.2 |
| Race/ethnic background | | |
| White/Caucasian | 9 | 81.8 |
| Asian/Indian | 2 | 18.2 |
| Fitzpatrick | | |
| II | 1 | 9.1 |
| III | 9 | 81.8 |
| IV | 1 | 9.1 |

40-800 Pa), whereas gels with high flexibility (typical range, 5%-1500% strain), measured with xStrain, can withstand more dynamic movement (stretch and relax).^{2,4} HA_{CON} is made with XpresHAN Technology containing 100% high molecular weight (HMW) HA species with 7% butanediol diglycidyl ether (BDDE) crosslinking, providing moderate *G'* (171) and high flexibility (xStrain: 930). HA_{JVOL} is made with Vycross Technology containing 90% low molecular weight and 10% HMW HA species with 6% BDDE crosslinking, providing a moderately high *G'* (307) and low flexibility (xStrain: 179).^{2,4}

Differences in rheological properties (eg, *G'* and xStrain) result in HA fillers that have unique clinical behaviors once injected, such as lifting capacity, tissue integration, and dynamic support. The current study compared the clinical behaviors of HA_{CON} and HA_{JVOL} by evaluating and comparing (1) product integration and dynamic support and (2) lifting capacity (volumization) of both fillers through ultrasound imaging and clinical photography with 3D volume change analyses.

METHODS

Study Design

This was a 12-month, randomized, split-face, single-center US study (July 2022-July 2023) comparing 2 HA fillers (Restylane Contour [HA_{CON}], Galderma and Juvederm Voluma [HA_{JVOL}], Abbvie/Allergan Aesthetics). There were 5 study visits (Day 0, Months 1, 6, 9, and 12) with injection at Day 0 and touch-up at Month 1 to midface until optimal correction was reached in agreement with the patient and treating investigator on both sides of the face separately. Products were injected medially and laterally into the cheek/midface region along the plane of the zygomatic arch (~1 cm medial to hairline) below the superficial musculoaponeurotic system layer at the supraperiosteal to subcutaneous region using a 25 G Softfil cannula (40 mm) with EasyGuide (Prolenium Medical Technologies Inc., Ontario, Canada; Figure 1). Two pilot holes were used for injections. The lateral injection pilot

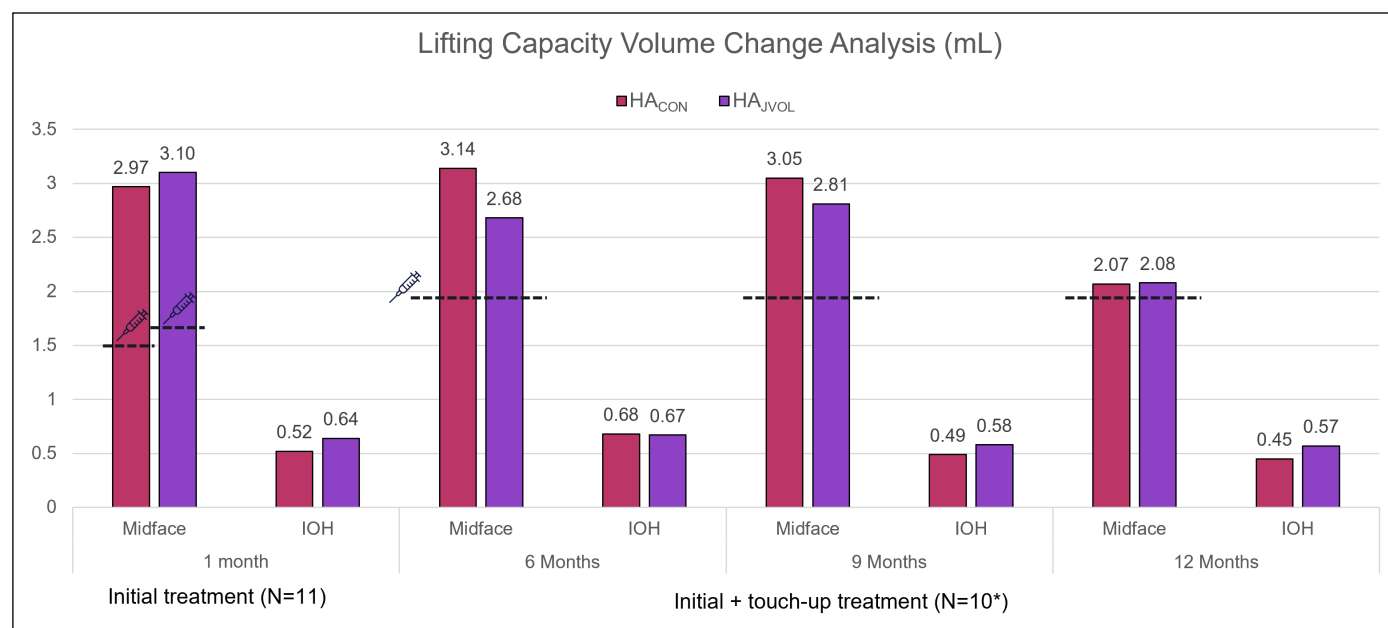


Figure 2. Lifting capacity (volumization) measured by 3D imaging volume change compared with baseline analysis. The syringe with a dotted line represents average injected amount (mL) in each group for initial and Month 1 touch-up. Touch-up for both groups was after the 1-month assessments. Initial treatment volume was 1.5 and 1.6 mL for HA_{CON} and HA_{JVOL}, respectively. Total treatment volume (initial + optional 1-month touch-up treatment) was 1.9 mL for both HA_{CON} and HA_{JVOL}. No product injected in the infraorbital hollows. One patient was removed from the average initial + touch-up volume and thus from 6-, 9-, and 12-month analyses because of protocol violation.

Table 3. Lifting Capacity (Volume Change) Ratios Comparing the 3D Imaging Volume Change Compared with Baseline Analysis with the Injection Volumes

| | | Month 1 | | Month 6 | | Month 9 | | Month 12 | |
|---------|--|-------------------|--------------------|-------------------|--------------------|-------------------|--------------------|-------------------|--------------------|
| | | HA _{CON} | HA _{JVOL} | HA _{CON} | HA _{JVOL} | HA _{CON} | HA _{JVOL} | HA _{CON} | HA _{JVOL} |
| Midface | Total volume change (mL) | 2.97 | 3.10 | 3.14 | 2.68 | 3.05 | 2.81 | 2.07 | 2.08 |
| | Mean ratio ^a | 2.09 | 1.94 | 2.08 | 1.40 | 1.72 | 1.72 | 1.02 | 1.32 |
| | P-value (HA _{CON} vs HA _{JVOL}) | 0.4096 | | 0.0534 | | 0.9780 | | 0.2078 | |
| IOH | Total volume change (mL) | 0.52 | 0.64 | 0.68 | 0.67 | 0.49 | 0.58 | 0.45 | 0.57 |
| | Mean ratio ^a | 0.37 | 0.43 | 0.51 | 0.39 | 0.29 | 0.35 | 0.25 | 0.33 |
| | P-value (HA _{CON} vs HA _{JVOL}) | 0.4962 | | 0.4416 | | 0.5132 | | 0.1302 | |

HA, hyaluronic acid; IOH, infraorbital hollow. ^aLifting capacity ratios for each patient were calculated using the total volume change (mL)/injected amount (mL) and averaged for the mean ratio.

hole was placed 1 cm from the lateral canthus at the intersection of a horizontal line from the alar base insertion. The medial injection pilot hole was placed 1 cm lateral from the tail of the brow at the intersection of a horizontal line from the nares to the top of the tragus. The product was not allowed in the ZCL/tear trough area. The study followed good clinical practice, and all patients provided written informed consent. The study was approved by the Sterling Institutional Review Board and registered at [Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT05622851): NCT05622851.

Population

Females or males aged 22 to 65 years were eligible to participate if they had midface volume loss and contour deficiency (investigator

opinion); they could be any race/ethnicity and have any Fitzpatrick skin type. Exclusion criteria included pregnancy or breastfeeding; history of allergy or hypersensitivity to lidocaine and/or injectable HA; previous permanent or semi-permanent implant in the proposed treatment area; previous biodegradable tissue augmentation therapy in the proposed treatment area within 12 months prior to the baseline visit; or other facial/treatment procedure in treatment area within 6 months of the baseline visit.

Assessments

Efficacy assessments included standardized digital clinical photography (VISIA, Canfield Scientific, Fairfield, NJ) and 3D imaging (VectraH2 3D,



Figure 3. 2D clinical photographs of Patient 1: female Caucasian patient, aged 38 years, with Fitzpatrick skin type (FST) III treated with 2.6 mL HA_{CON} (right side) and 3.4 mL HA_{JVOL} (left side). Photographs from baseline, Months 1, 6, and 12. (A-E) Frontal view, (F-J) three-quarter right, and (K-O) three-quarter left.

Canfield Scientific, Fairfield, NJ) at baseline preinjection, Month 1 pretouch-up, and Months 6, 9, and 12. Instructions were provided on adopting a neutral expression, a closed-mouth smile, and a maximum smiling expression (with 3 images for each: three-fourth front, front, and three-fourth left) under standard lighting for 2D imaging. Neutral expressions were captured with a 3D system utilizing raised flash to provide raked lighting to better capture and view skin topography and contours. Its software allows 3D viewing of the images and quantitative assessment of facial parameters. Topographic volumetric changes (ie, lifting capacity in mL) for each cheek/midface and infraorbital hollow (IOH) were analyzed by Canfield Scientific imaging analysis

experts (left and right cheeks separately; [Figure 1](#)). Note that although injections were only performed in the cheek/midface region, IOH volumetric analyses were performed to evaluate the secondary effects of cheek/midface injections.

Ultrasound assessments were performed using an 18 MHz Venue Fit (GE HealthCare, Chicago, IL) ultrasonic transducer at baseline and all time points, with the addition of immediately postinjection on Day 0, to assess tissue behavior following treatment, including product integration and flexibility. Ultrasound images were taken on each patient's left and right cheeks (ie, medial zygomatic arch), at neutral expression, and videos of a maximum smiling expression (neutral

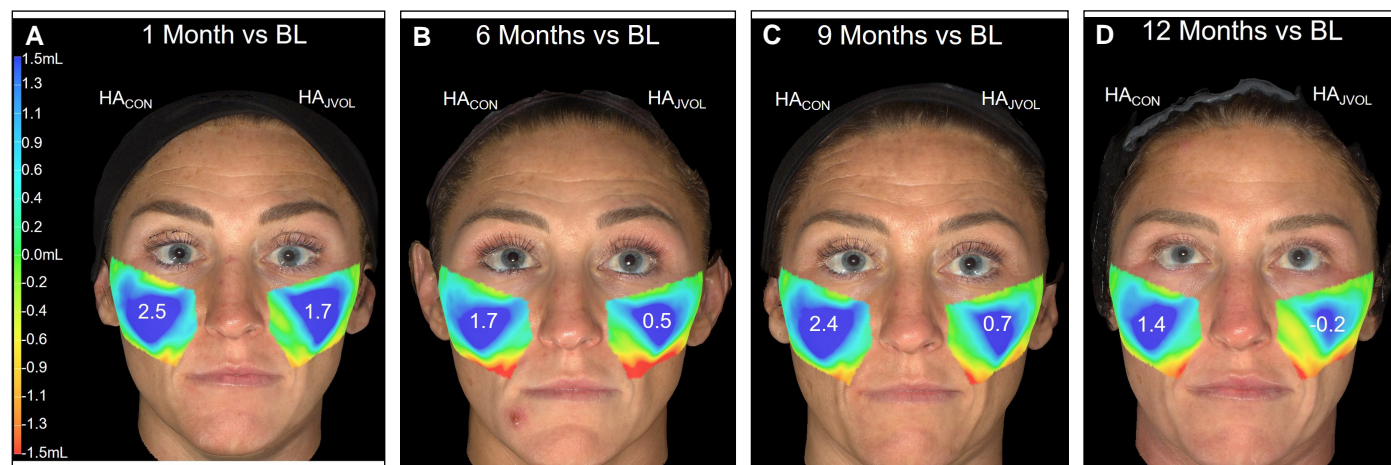


Figure 4. Heat map lifting capacity imaging analyses for Patient 1: female Caucasian patient, aged 38 years, with FST III treated with 2.6 mL HA_{CON} (right side) and 3.4 mL HA_{JVOL} (left side). Lifting capacity (volume change) from baseline at Months 1 (A), 6 (B), 9 (C), and 12 (D). Numbers represent the total volume change (mL) calculated for each midface region (green or blue represents increased volume, and yellow to red represents decreased volume). BL, baseline.

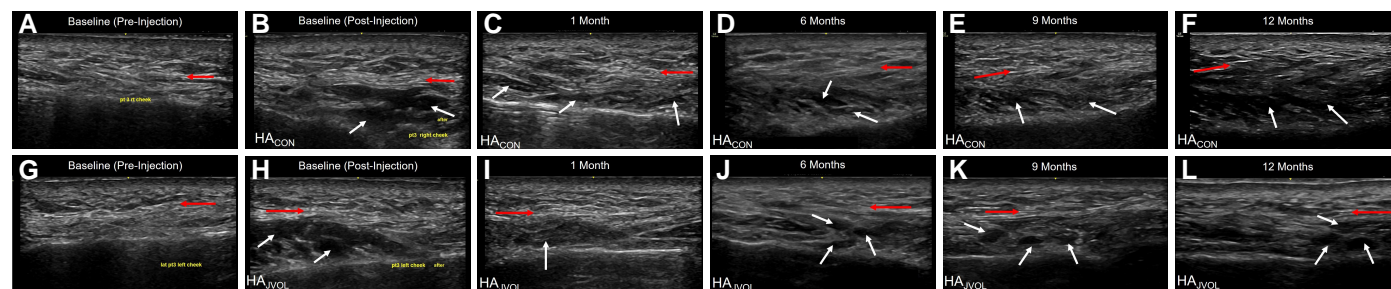
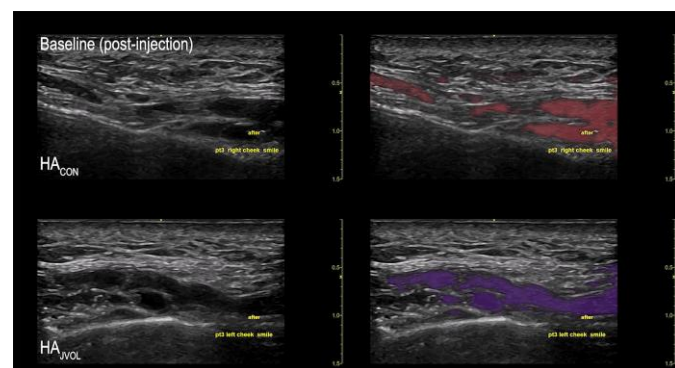
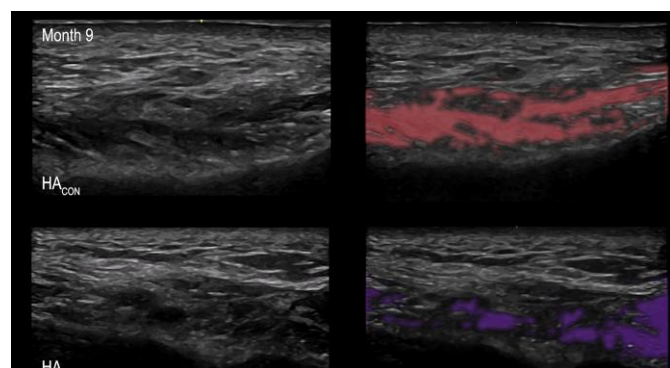


Figure 5. Ultrasound images for Patient 1: female Caucasian patient, aged 38 years, with FST III treated with 2.6 mL HA_{CON} (right side) and 3.4 mL HA_{JVOL} (left side). (A-F) HA_{CON} treated side at all time points. (G-L) HA_{JVOL} treated side at all time points. Red arrows (top arrow) point to the superficial musculoaponeurotic system layer, and white arrows (bottom arrows) are examples of hyaluronic acid filler aggregates.



video 1. Watch now at <http://academic.oup.com/asjopenforum/article-lookup/doi/10.1093/asjof/ojaf006>



video 2. Watch now at <http://academic.oup.com/asjopenforum/article-lookup/doi/10.1093/asjof/ojaf006>

to maximum smile) were also captured. The placement of the ultrasound probe was at the same location of the product injection to ensure consistent assessment across patients.

Safety assessments included collection of any unexpected adverse events, including anything other than minor and temporary redness, swelling, and bruising at the injection site, by the treating investigator throughout the study after each treatment.

Statistical Analysis

Data of completing patients were included for all statistical analyses. A descriptive statistical summary was performed, including mean, median, standard deviations, minimum, and maximum of values at all applicable time points and for both treatments. For 3D imaging analyses, data were normalized for differences in average volume

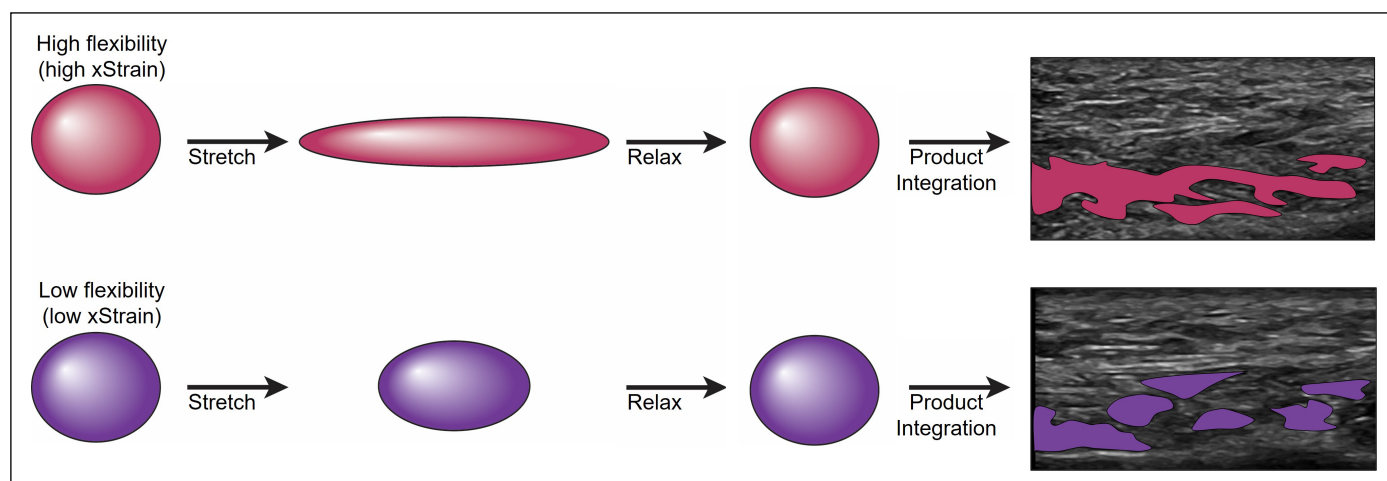


Figure 6. Proposed mechanism for how hyaluronic acid (HA) filler flexibility (xStrain) correlates to postinjection clinical performance. HA fillers with high flexibility can stretch and relax (return to shape) during dynamic facial movements, slowly integrating into the tissue over time by stretching into smaller tissue cavities while still maintaining flexibility for dynamic movement. HA fillers with low flexibility would not move very much with dynamic facial movements and would not appear to integrate into the tissues very well, staying the same size and shape over time. Ultrasound images are from the same patient in [Figure 3](#) taken at 9 months postinjection.

injected per patient by calculating the mean of the ratios to statistically compare lifting capacity to injected amount (mL:mL). A paired *t* test was used to analyze change from baseline, and a Wilcoxon rank-sum test or sample *t* test was used to compare study treatments.

RESULTS

There were 11 patients enrolled in the study and 1 patient withdrew because of a pregnancy (protocol violation) between the Months 1 and 3 visit. Baseline characteristics for study patients ($n = 11$) are presented in [Table 1](#). The mean age was 46 years (range, 32–61 years) and most patients were female (81.8%) and White/Caucasian (81.8%). As shown in [Table 2](#), average total injected volumes ($n = 10$) were equivalent (1.9 mL HA_{CON}; 1.9 mL HA_{JVOL}) with more product injected medially vs laterally (1.5 vs 0.4 mL).

Efficacy

Analysis of 3D imaging showed that lifting capacity (mL, volume change compared with baseline) with both products was approximately double the average initial injected amount at 1 month ([Figure 2](#); HA_{CON}: 2.97 mL and HA_{JVOL}: 3.10 mL). After touch-up, a higher lifting capacity compared with the average total injected amount was sustained through Month 12 for both products ([Figure 2](#); HA_{CON}: ≥ 2.07 mL and HA_{JVOL}: ≥ 2.08 mL). From Months 6 to 9, the lifting capacity for HA_{JVOL} showed a slight increase, rising from 2.68 to 2.81 mL. However, the overall trend indicated a decrease in lifting capacity over the 12-month period. Additional analyses showed that as a secondary benefit of injecting the cheek/midface region, both products demonstrated about 0.5 mL lifting capacity in the IOH region throughout 12 months.

When the 3D imaging data were normalized for injected amounts (lifting capacity ratios), there were no significant differences in the midface (*P*-value range, .0534–.9780) and IOH (*P*-value range, .1302–.5132) lifting capacity between the 2 treatment groups at all time points ([Table 3](#)).

Representative patient photographs show results through 12 months, and 3D imaging analyses heat maps show overall lifting capacity (volume change) compared with baseline at all time points for both sides of the face ([Figures 3, 4](#)). Trending observations with ultrasound show that the products behaved differently once injected. HA_{CON} gradually integrated (dispersed) within the tissue over 12 months and stretched and elongated during a smiling expression and returned to a neutral position, demonstrating dynamic support and flexible movement. HA_{JVOL} aggregates tended to remain consistent in size and shape during both neutral and smiling expressions, demonstrating low dynamic support and flexibility. Representative patient ultrasound photographs ([Figure 5](#)) and videos ([Videos 1, 2](#)) demonstrate these trending observations.

Safety

No unexpected adverse events were reported or observed during the study period.

DISCUSSION

Individuals seeking to counteract signs of facial aging typically desire immediate and natural-looking visual effects along with long-lasting results and a good safety profile. To help patients get this desired outcome, it is important for HA fillers to optimally add volume and integrate into the skin, adapting to facial movements with favorable dynamics.^{2,5} Two important rheological properties, *G'* (gel strength/firmness) and xStrain (flexibility), are good predictors of these behaviors.² *G'* (gel strength/firmness) contributes to a gel's ability to create lift and volumization, whereas flexibility (xStrain) is a desirable characteristic for adapting to dynamic facial movements.²

The current study uses 3D photography and ultrasound to show how differences in rheological properties can correlate with the clinical performance of 2 different midface HA fillers, HA_{CON} and HA_{JVOL}. To our knowledge, only 2 other studies have used ultrasound to compare the integration of HA fillers with different rheological

properties.^{6,7} However, our study expanded upon those ultrasound capabilities to offer unique and valuable insights into how these 2 HA fillers behave under dynamic facial expressions.

The observations with ultrasound photographs and videos demonstrated that with higher xStrain (flexibility), HA_{CON} had more distributed product integration and greater ability to stretch and relax with dynamic facial expressions compared with HA_{JVOL}, which remained as consistently sized aggregates exhibiting low dynamic flexibility. Figure 6 shows a proposed mechanism for how HA filler flexibility (xStrain) correlates to postinjection clinical performance. The ultrasound data demonstrated that HA fillers with high flexibility (xStrain) can stretch and return to their original shape during dynamic facial movements. Over time, they gradually integrate into the tissue by stretching into smaller cavities while maintaining flexibility. In contrast, HA fillers with low flexibility do not move as much with facial expressions and tend to remain the same size and shape, showing less integration into the tissues.

Additionally, both products demonstrated comparable lifting capacities in the cheek region (Figure 2; HA_{CON}: ≥ 2.07 mL and HA_{JVOL}: ≥ 2.08 mL) and IOH region (Figure 2; HA_{CON}: ≥ 0.45 mL and HA_{JVOL}: ≥ 0.57 mL) throughout the 12-month period with no significant differences between the lifting capacity ratios ($P > .05$). Of note, the data consistently demonstrate a lifting effect (~ 0.5 mL) in the IOH region, even though injections are administered solely in the cheek area, suggesting that treating the cheeks can effectively disguise hollowing in this area. At Month 1, the cheek lifting capacity was about double the amount of injected volume, which might be explained by the hygroscopic nature of HA filler products.⁴ Over the 12-month period, there was a decrease in lifting capacity for both products, aside from HA_{JVOL} having a slight increase from Months 6 to 9 (2.68–2.81 mL) in cheek lifting capacity. This variation could be explained by various factors, including minor differences in facial positioning for photographs. Overall, these data demonstrated that despite having a lower G' , HA_{CON} still maintained a similar lifting capacity compared with HA_{JVOL}. Although G' is generally a good predictor for a gel's lifting capacity, there could be other factors contributing to this clinical observation.^{2,4} In this instance, 1 possible explanation is that HA_{CON} has a large particle size, contributing to its lifting capacity and volumization capabilities.⁵

Combining the observational ultrasound data with the quantitative lifting capacity analyses, we saw that although HA_{CON} had higher integration into the tissue, this did not affect the product's lifting capacity and ability to volumize. This suggests that more distributed product integration does not relate to product migration into other regions, but distribution into smaller tissue cavities within the same region. Various literature demonstrates that flexible HA fillers with distributed tissue integration patterns tend to provide natural-looking results.^{3,5,8-10}

We believe this study provides valuable insights and clinical implications but acknowledge that the sample size was relatively small, which may limit the generalizability of the findings. However, the split-face design enhances the power of the side-by-side product comparisons. We also recognize the limitations of using descriptive ultrasound imaging instead of quantitative methods. In this scenario, higher resolution is necessary to accurately quantify aggregate size, but higher frequency ultrasounds, which provide better resolution, are unable to penetrate to the required depth. To further validate these findings, future research should include a larger sample size and quantitative ultrasound imaging for superficial injections in a different anatomical region.

CONCLUSIONS

Two rheologically distinct midface fillers, HA_{CON} and HA_{JVOL}, demonstrated a similar duration of lifting capacity through 12 months. However, HA_{CON}, which has a higher xStrain (flexibility), exhibited more distributed product integration and flexibility (stretch and relax) to support dynamic expressions. These data demonstrate a correlation between rheological characteristics and clinical performance, highlighting the value for injectors in understanding how they intersect to aid in product choice based on anatomical area, injection depth, and patient characteristics.

Disclosures

Dr Weiner is a speaker, trainer, advisor, and researcher for Galderma (Lausanne, Switzerland). He received honorarium, for this research from Galderma. Drs Hicks, Nguyen, and Meckfessel are employees of Galderma.

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