The Role of Clinical Examination in Midface Volume Correction Using Hyaluronic Acid Fillers: Should Patients Be Stratified by Skin Thickness?

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Abstract

Background: Aesthetic physicians have several hundred injectable products to select from. Due to differences in their manufacturing technology, these products display varying biophysical qualities, such as their cohesivity and lift capacity. Currently, there is no guidance to objectively selecting the best product for a particular patient. Therefore, an algorithmic approach is required to take specific skin characteristics into consideration.

Objectives: To evaluate (1) whether subjects seeking injectable treatments for midfacial volume loss and/or contour deficiency can be stratified based on specific skin characteristics (e.g., thickness, fat quantity, bony structure) and (2) whether particular hyaluronic acid fillers perform best when used in such particular strata.

Methods: This was a prospective, Phase IV, open-label, single-center clinical trial. Thirty female patients with midface/cheek volume loss and/or contour deficiency were recruited (mean age, 53.5 years; SD, 12.57; range, 35–75 years). Subjects were treated with either Restylane Lyft (HAL) or Restylane Volyme (HAV) and followed for 4 months post-injection. Treatment allocation was based on the treating physician’s clinical evaluation and compared with ultrasound evaluation. Ultrasound images were used to confirm stratification. Safety and efficacy assessments were performed at each study visit: baseline, week 2, week 4, week 8, and week 16. Subgroup analyses evaluated whether particular strata performed best when treated with specific products.

Results: The 2 investigative products varied in their efficacy, depending on the characteristics of the subject.

Conclusions: The use of a treatment algorithm may improve outcomes for patients seeking injectable treatments for midfacial volume loss and contour deficiencies.

Level of Evidence: 2

Editorial Decision date: January 27, 2020; online publish-ahead-of-print February 6, 2020.
Nonsurgical aesthetic procedures for rejuvenation of the face include injectables such as botulinum toxin and soft tissue fillers. These treatments are the most common aesthetic procedures performed worldwide. Of the over 150 injectable fillers available on the market today, hyaluronic acid (HA)-based injectables are the most commonly used, with over 1.26 million treatments performed worldwide each year. Moreover, it is likely that these numbers are underestimated, as in 2017 over 722,394 HA injections were performed in the United States alone. Restylane ([HAₚ], Galderma Laboratories, L.P., USA) was the first HA to gain FDA approval in 2003. The HAₚ line of dermal fillers offers a wide range of products (2 of which are Restylane Lyft (HAₚ) and Volyme (HAₚ)), both Galderma Laboratories, L.P., USA), available for administration using varying injection techniques, to treat multiple indications. Currently, product choice and amount of volume used for injectable procedures varies between physicians, as there is no standard for treatment. This inherent weakness is also a strength in aesthetic medicine, as it allows physicians to combine science and art to personalize patient outcomes. In most cases, individual assessment based on the injector’s preference and experience determines final product selection and technique. As accurate facial analysis and product choice are key to ensuring optimal aesthetic outcomes, a standard of assessment is required to establish best practices between injectors and to better regulate the use of dermal fillers in aesthetic medicine.

**HAₚ Product Descriptions**

HAₚ and HAᵥ are HA gels containing lidocaine. The HA concentration of both products is consistent (ie, 20 mg/mL), but the products differ in their particle size. HAₚ has the largest gel particle size in the family (ie, 10,000 particles/mL) to provide more lifting, filling, and volumization; and HAᵥ has medium-sized particles to provide volume with diffuse tissue integration. The 2 products also differ in their manufacturing technology, which impacts their biophysical characteristics. HAₚ is manufactured using non-animal stabilised HA (NASHA) technology, which creates a firm and cohesive gel with a high G-Prime (G’, ~600 pa) and very high lift capacity, whereas HAᵥ is manufactured using Optimal Balance Technology (OBT/XpresHA technology), which creates a softer, more viscous gel texture with a lower G’ (~200 pa) and moderate to high lifting capacity. Both HAₚ and HAᵥ are available in the United States, and Canada.

In the present study, researchers investigated how an understanding of the patient’s skin characteristics (eg, thickness, volume, projection, elasticity) alongside the biophysical characteristics of different fillers (ie, HAₚ and HAᵥ), could improve treatment outcomes (eg, injection volumes, aesthetic outcome, complication rates). The investigators proposed that in order to optimize aesthetic outcomes, treatment assignment (ie, HAₚ or HAᵥ) should reflect the relationship between the subjects’ tissue and characteristics of the selected product. For example, using a higher G’ such as HAₚ on patients with thin skin may result in palpable product, creating visible contour irregularities. Therefore, subjects with thin skin would be better treated with a product with more tissue integration, such as HAᵥ. However, in patients with thick skin, HAᵥ may not provide enough lifting to sufficiently correct their volume loss, thus, they may have better aesthetic outcomes when treated with HAₚ.

In order to validate this proposed treatment algorithm (Figure 1), subjects in the present study were assigned to one of the 2 strata based on clinical examination and treated accordingly. Group A consisted of subjects with poor structural support and volume (eg, atrophy of soft tissues, loss of projection), but with an adequate skin envelope (ie, thick skin); and Group B consisted of subjects with poor structural support and volume and with a poor skin envelope (ie, thin skin). Subjects assigned to Group A were treated with HAₚ and subjects assigned to Group B were treated with HAᵥ. Subjects were then followed up for 4 months post-injection.

**Study Question**

For subjects seeking injectable treatments for facial volume loss and/or contour deficiency of the midface, is it clinically beneficial to stratify them based on their skin characteristics, in order to select the ideal product (ie, HAₚ or HAᵥ)?

**Primary Endpoint**

The primary endpoint of this study was the change from baseline between the 2 HA products at Week 16 post-injection, using the physician-assessed Global Aesthetic Improvement Scale (GAIS) as a measure for treatment efficacy.

**Secondary Endpoints**

Secondary endpoints of this study included the comparison of 2 HA products in the treatment of midface/cheek deformities at all visits. This endpoint required the evaluation of multiple safety and efficacy assessments, including: (1) physician-assessed efficacy using the GAIS scale; (2) Medicis Midface Volume Scale (MMVS) scores based on blinded review; (3) the patient satisfaction questionnaire (PSQ); (4) ultrasound evaluations; and (5) adverse events (AEs).
METHODS

Study Design

This study was conducted in accordance with ethical principles having originated from the contents of the Declaration of Helsinki,\(^7\) that are consistent with “Good Clinical Practice” ICH Tripartite Guidelines and the applicable laws and regulations of Canada.\(^8\) The current investigators, protocol, consent form and all associated research documentation and procedures were fully approved by a centralized research ethics board prior to the commencement of any study-related activities. This study was fully approved by the external research ethics board “Institutional Review Board (IRB) Services.”

This was a prospective, Phase IV, single-center clinical trial that took place at the Victoria Park Clinical Research Unit (Westmount, Quebec, Canada) from December 2017 until December 2018. A total sample size of 30 patients over the age of 30 with midface/cheek volume loss and/or contour deficiency were recruited for this study, providing 60 unique hemiface observations.

Subjects were treated with either HA\(_L\) or HA\(_V\) and followed up for 4 months post-injection. Throughout this time, various safety and efficacy assessments were performed during each of the following 5 study visits: Visit 1 (Baseline); Visit 2 (Week 2 ± 5 days); Visit 3 (Week 4 ± 5 days); Visit 4 (Week 8 ± 5 days); and Visit 5 (Week 16 ± 5 days).

Eligibility Criteria

The main inclusion criteria included female sex, given the known sex-based differences in the skin’s matrix.\(^9\)

Figure 1. (A, B) The “Mid- and Lower-Face Algorithm (MLFA)” for facial rejuvenation.
between the ages of 30 and 75 years old, given the known age-related differences in dermal features 9,10; established midface/cheek hollowing, based on the investigator’s opinion; and an MMVS score of 2 or 3 at baseline. The main exclusion criteria included current pregnancy or lactation; hypersensitivity to HA products, HA fillers or amide local anesthetics; and skin thickness in the treatment areas between 1.29 and 1.49 mm (ie, “normal” thickness), as determined by ultrasound at baseline, to ensure no overlap between the 2 strata (ie, thin and thick skin). For a full list of the inclusion and exclusion criteria, visit clinicaltrials.gov and use the search identifier: NCT03381040.

Procedures

During Visit 1 (Baseline), subjects first read and signed an informed consent form before any study-related activities were performed. Then, a full medical history was taken, including a list of their current medications and concomitant diseases. Women of childbearing potential underwent a urine pregnancy test, to rule out concurrent pregnancy. Standardized 3D photographs (Vectra M3, Canfield Scientific) were then taken and a blinded evaluator rated their midface volume loss based on the MMVS. A description of all physician- and patient-assessed questionnaires is presented in Supplementary Appendix A, available online at www.asjopenforum.com. Clinical examination involved palpation and the evaluation of variables such as (a) the skin envelope thickness (ie, thin, normal, thick); and (2) the quantity and quality of the subcutaneous tissue. Based on clinical examination (eg, visual assessment, palpation, Slide- and Pinch Tests), the injecting physician allocated subjects to treatment group, marked the injection sites and left the room.

Group Assignment

Our study design utilized nonrandom group assignment, aimed specifically at maximizing the differences in group mean skin thickness, while minimizing other subject characteristics. The use of both products in each subgroup was not included in the present study, given the findings of previous histological research, which revealed the products’ different levels of tissue integration.11 Upon clinical examination, the use of NASHA in thin-skinned patients would have resulted in palpable product. This is primarily due to its targeted tissue integration. Conversely, OBT allows for its use even in thin-skinned patients because it has diffuse product integration. Therefore, subgroups were not treated with both products as histological studies support an increase of adverse events and unfavorable results (eg, palpable product in thin-skinned individuals and lack of efficacy in thick-skinned subjects).11

After group assignment, a blinded ultrasound technician then performed ultrasound examinations at the indicated sites. All bilateral ultrasound evaluations of the injection areas were taken using a high-frequency ultrasound (EPISCAN-I-200, Longport Inc.). Following ultrasound evaluations, the injecting physician returned and performed the treatments, as he had previously assigned. The injecting physician remained blinded to the results of the ultrasound until all study-related procedures were complete and data analyses began. Three-dimensional images displaying the marked treatment sites were consulted to ensure consistent placement of the ultrasound probe during assessments, at subsequent visits.

Subjects were seen at Weeks 2 (Visit 2), 4 (Visit 3), 8 (Visit 4), and 16 (Visit 5) for follow-up visits. At Week 2, a second optional treatment was available to subjects who, in the investigator’s opinion, had not yet reached their optimal aesthetic outcome. All subjects treated at Week 2 received the same product as at Baseline. At all follow-up visits, the following procedures were performed: 3D photography, GAIS, MMVS, PSQ, clinical examination, and ultrasonography. Treatments were not performed at Visits 3, 4, or 5. The GAIS scale was always assessed by the injecting physician, the MMVS was always scored by the same blinded evaluator and all ultrasound images were taken and analyzed by the same operator.

Injection Technique

All injections were performed by a single injector and board-certified plastic surgeon (A.N.). Treatment areas included the overlapping regions of zygomatic, submalar, and anteromedial cheek (Figure 2). Volumes of product used varied between subjects and often within subjects (bilaterally), given the natural asymmetry of the face. Volumes used were limited to achieving anatomic correction, up to a maximum of 2 cc per treatment session per side. This maximum volume was in accordance with the recommended dosage indicated within the product monographs.5,6 Subjects were treated with the aim of achieving at least a 1-point improvement on the MMVS.12 Injections were performed with sterile 27G × ½ needles, using a slow injection technique and careful aspiration. Product was placed in the deep subcutis tissues of the 3 overlapping regions, for both groups.

Statistical Methods

The program SPSS Statistics (version 20.0) was used for all data analyses. All evaluations were considered in the assessment of product safety and efficacy. Continuous
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**RESULTS**

**Subject Characteristics**

Thirty female patients were recruited. Based on clinical examination (eg, visual assessment, palpation), 17 subjects were characterized as having thick skin and subsequently treated with HA\(_L\) (56.6%); and 13 subjects were characterized as having thin skin and treated with HA\(_V\) (43.3%). The mean age of the sample was 53.5 years (SD, 12.57; range, 35–75 years). The mean age of the HA\(_L\) group was 49 years (SD, 10.12) and the mean age of the HA\(_V\) group was 58 years (SD, 13.98). An independent t-test revealed that the age differences between the groups were not statistically significant \([t(25) = -1.457; p = 0.157]\). Figures 3 and 4 depict examples of treatment effect in thin- and thick-skinned subjects.

**Ultrasound Determination of Dermal Thickness**

Following treatment, ultrasound was used to corroborate the clinical examination (Figures 5 and 6). Based on the analyses of ultrasound images, dermal thickness significantly correlated with the treatment group (right side: Pearson = −0.772; \(p = 0.000\); left side: Pearson = −0.831; \(p = 0.000\)). Subjects treated with HA\(_L\) had statistically significant thicker skin in their bilateral cheeks (right side: \(M = 1.69, SD = 0.24\); left side: \(M = 1.74, SD = 0.28\)) than those treated with HA\(_V\) (right side: \(M = 1.18, SD = 0.21\); left side: \(M = 1.23, SD = 0.25; p > 0.00\)).

**Statistical Power**

Using an effect size based on the means and standard deviations of the groups’ skin thicknesses at baseline, a G*Power calculation revealed that the present study has a power of 0.63. This value equates to a study with moderate statistical power.

**Follow-up and Attrition Rates**

The overall mean time of follow-up for subjects was 112.42 days (range, 108–125 days). By visit 5 (week 16), the dropout rate was 13.33% (\(n = 4/30\)). Two of the patients who dropped out were treated with HA\(_L\) (\(n = 2/17; 11.76%\)) and 2 were treated with HA\(_V\) (\(n = 2/13; 15.38%\)).

**Adverse Events**

There were no reported serious AEs throughout the duration of the trial. All AEs were mild to moderate in severity and transient in nature. They included AEs typically...
associated with injection (eg, swelling, bruising) and none was related to the products. Adverse event incidence rates are presented in Table 1. In total, there were 3 cases of bruising (10%) and 4 cases of swelling (13.33%).

**Primary Endpoint**

**Difference in Physician-Assessed Efficacy Between 2 HA_R Products at Week 16 (Visit 5) in Comparison to Baseline (Visit 1), Using the GAIS Scale**

As can be seen in Table 2, at Week 16 post-injection, there were differences in midfacial improvement between subjects treated with HA_L and HA_V, as per the physician-assessed GAIS scale. A Chi-square goodness-of-fit test revealed that the proportion of responses in each category of the GAIS significantly differed between groups at Week 16 ($\chi^2 = 476.662.78; \text{df} = 3; p = 0.000$). The evaluator rated that the majority of patients treated with HA_L had “much improved” ($n = 8/17; 57.1\%$), whereas the majority of those treated with HA_V had “improved” ($n = 6/13; 54.5\%$). This may be due to the greater product integration of HA_V, which results in a more natural effect (compare Figures 5 and 6).

**Secondary Endpoints**

**Difference in All Measures Between 2 HA_R Products at All Visits**

Results of the GAIS, PSQ, and MMVS are displayed by group in Table 3, for all visits. For analyses, ordinal logistic regressions were performed to examine the relation between treatment group, visit number (independent
variables), and scores on the GAIS and PSQ (dependent variables). Chi-squared tests of independence were performed using the likelihood ratio to examine the relation between the treatment group (independent variable) and raw scores of the MMVS (dependent variable) at Baseline, as well as treatment group and response rates at Visit 5.

**Global Aesthetic Improvement Scale**

Ordinal logistic regression analyses revealed that GAIS scores were not significantly predicted by group or visit number \( (p > 0.05; \text{ Table 3}) \). High rates of aesthetic improvement were noted in both groups, with the injecting physician rating >75% of subjects as having at least “improved” outcomes, throughout the entire duration of the study. There were no cases of a “worse” global aesthetic appearance.

**Medicis Midface Volume Scale**

Prior to treatment, groups were similar in terms of the amount of midfacial volume loss and/or contour deformity found in the samples, as the relation between the treatment group and MMVS scores was insignificant \( \chi^2 (2, N = 27) = 3.580, p = 0.167 \). The frequency distribution of MMVS scores did not significantly vary between the 2 groups, at baseline.

Following the second treatment (ie, Visit 3/Week 4), the blinded reviewer noted a one-point improvement in 56.25% of subjects \( (n = 13.5/24) \). Maximum MMVS response rates (~75%) were noted between Visits 4 (Week 8) and 5 (Week 16). There were no cases throughout the duration of the study of a negative MMVS response (ie, appearance of midface volume loss and/or contour deficiency worsening). The maximum MMVS response rate observed was a one-point improvement; there were no cases of a 2- or 3-point increase.

At Visit 5/Week 16, subjects treated with either HA\(_L\) or HA\(_V\) had similar improvements in their midfacial volume and/or contours. The relation between treatment group and MMVS response rate was insignificant \( \chi^2 (2, N = 24) = 0.087, p = 0.768 \). The frequency distribution of MMVS response rates did not significantly vary between the 2 groups.

**Patient Satisfaction Questionnaire**

Patient satisfaction was assessed using the Patient Satisfaction Questionnaire (PSQ) at all follow-up visits.
The PSQ is a 5-point, patient-rated scale comprising of “extremely satisfied,” “satisfied,” “slightly satisfied,” “dissatisfied,” and “extremely satisfied.” The PSQ was a paper-based questionnaire that was distributed by the study coordinator. It was anonymized as subjects were identified only by their subject numbers. The treating physician was not present during the subjects’ evaluations and remained blinded to their responses. Ordinal logistic regression analyses revealed that PSQ scores were significantly predicted by group ($p = 0.007$), but not by visit number ($p > 0.05$; Table 3). Subjects treated with HA$_L$ reported higher levels of satisfaction than those treated with HA$_V$.

### Ultrasound Evaluations

#### Correlations Between Subjective Clinical Examination and Objective Ultrasound Evaluations

Ultrasound classified 5/17 (29.4%) subjects as having thick skin, despite clinical examination identifying them as having thin skin; and it classified 4/13 (30.7%) subjects as having thin skin, despite clinical examination identifying them as having thick skin. Therefore, objective ultrasound assessments and subjective clinical examination resulted in similar findings approximately 70% of the time.

#### Global Aesthetic Improvement Scale, MMVS, and PSQ Subgroup Analyses

During post-hoc analyses, data at Visit 5/Week 16 were further analyzed based on the following 4 subgroups:

1. HA$_L^+$ = Subjects with correctly identified thick skin, treated with HA$_L$ ($n = 12$);
2. HA$_L^-$ = Subjects with thin skin, incorrectly identified as having thick skin, treated with HA$_L$ ($n = 3$);
3. HA$_V^+$ = Subjects with correctly identified thin skin, treated with HA$_V$ ($n = 3$);
4. HA$_V^-$ = Subjects with thick skin, incorrectly identified as having thin skin, treated with HA$_V$ ($n = 5$);

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**Table 1.** Adverse Events Present at Each Follow-Up Visit

| Tx group (n) | Visit | Bruising, n (%) | Swelling, n (%) |
|-------------|-------|-----------------|-----------------|
|             |       | Mild | Moderate | Mild | Mild |
| HA$_L$      | 2     | 0   | 1 (5.8) | 2 (11) | |
| 17          | 3     | 1 (5.8) | 0 | 0 |
| HA$_V$      | 2     | 1 (7.6) | 0 | 2 (7.6) |
| 13          | 3     | 0 | 0 | 0 |

AEs were not present at Visits 4 or 5. Visit 2, week 2; Visit 3, week 4; n, frequency; %, relative frequency for group.

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**Figure 6.** Ultrasound images from the cheek region of a female subject who was classified as having thick skin and treated with HA$_L$ at Baseline and Week 4. (A) Baseline and (B) right (week 4). A, membrane; B, gel; C, epidermis; D, dermis; E, subcutaneous region.
3. HA\textsuperscript{+} = Subjects with correctly identified thin skin, treated with HA\textsuperscript{+} (n = 7);
4. HA\textsuperscript{−} = Subjects with thick skin, incorrectly identified as having thin skin, treated with HA\textsuperscript{−} (n = 4).

Results of the GAIS, MMVS, and PSQ per subgroup are displayed in Table 2, for Visit 5/Week 16.

**Injection Volumes (Subgroups)**

The following mean volumes were used within each subgroup: HA\textsuperscript{+} = 1.33 cc (SD = 0.71; right side) and 1.26 cc (SD = 0.62; left side); HA\textsuperscript{−} = 1.50 cc (SD = 1.08; right side) and 1.52 cc (SD = 1.17; left side); HA\textsuperscript{+} = 1.40 cc (SD = 1.14; right side) and 1.32 cc (SD = 1.17; left side); and HA\textsuperscript{−} = 1.95 cc (SD = 0.36; right side) and 2.22 cc (SD = 0.89; left side). Values represent the mean volume administered between Visits 1 and 2. Results of a one-way non-parametric ANOVA (Kruskal-Wallis test) revealed that volumes did not statistically vary between subgroups [right side: $\chi^2(3) = 2.002$, $p = 0.572$; left side: $\chi^2(3) = 0.912$, $p = 0.823$]. From least to most product used, the mean ranks went in the order of: 1 = HA\textsuperscript{+}; 2 = HA\textsuperscript{−}; 3 = HA\textsuperscript{+}; and 4 = HA\textsuperscript{−}.
Global Aesthetic Improvement Scale (Subgroups)  
Results of a one-way non-parametric ANOVA (Kruskal-Wallis test) revealed that the distribution of GAIS scores varied across subgroups at Visit 5/Week 16 ($\chi^2(3) = 10.981, p = 0.012$). The mean ranks went in the order of: 1 = HA$_V$; 2 = HA$_L$; 3 = HA$_V$; and 4 = HA$_L$. Overall, high levels of satisfaction were reported by all subgroups, with only “extremely satisfied” and “satisfied” being reported by all subjects at Visit 5/Week 16.

Patient Satisfaction Questionnaire (Subgroups)  
Results of a one-way non-parametric ANOVA (Kruskal-Wallis test) revealed that the distribution of satisfaction scores was not statistically different across subgroups ($\chi^2(3) = 2.161, p = 0.540$). The mean ranks went in the order of: 1 = HA$_V$; 2 = HA$_L$; 3 = HA$_V$; and 4 = HA$_L$. Overall, high levels of satisfaction were reported by all subgroups, with only “extremely satisfied” and “satisfied” being reported by all subjects at Visit 5/Week 16.

Medicis Midface Volume Scale Grade (Right Side; Subgroups)  
Results of a one-way non-parametric ANOVA (Kruskal-Wallis test) revealed that the distribution of the MMVS response rates on the right side was the same across subgroups, at Visit 5/Week 16 ($\chi^2(3) = 2.470, p = 0.481$). While not significantly different, the mean ranks went in the order of: 1 = HA$_V$ and HA$_V$; 2 = HA$_V$; and 3 = HA$_L$, from most improvement to least.

Medicis Midface Volume Scale Grade (Left Side; Subgroups)  
Results of a one-way non-parametric ANOVA (Kruskal-Wallis test) revealed that the distribution of MMVS scores on the left side was the same across subgroups at Visit 5/Week 16 ($\chi^2(3) = 0.806, p = 0.848$). While not significantly different, the mean ranks went in the order of: 1 = HA$_L$; 2 = HA$_V$; 3 = HA$_L$; and 4 = HA$_V$, from most improvement to least.

DISCUSSION  
In the present study, investigators utilized treatment algorithm in an attempt to improve product selection for patients seeking injectable treatments for midfacial volume loss and contour deficiencies. This personalized approach consisted of a 2-step process: (1) Firstly, subjects were stratified based on their palpable skin characteristics (eg, skin thickness, subcutaneous fat quantity and positioning, bony structure); and then (2) they were assigned to receive a product based on its complementing biophysical characteristics. Several safety and efficacy assessments were performed during the 4 months post-injection, in order to validate this treatment algorithm.

Treatment Group Analyses  
Overall, both HA$_L$ products resulted in acceptable safety and efficacy assessments, throughout the duration of the study. Patients satisfaction, physician-assessed aesthetic improvement and blinded review all support that both HA$_L$ and HA$_V$ are safe and effective HA injectables for the indication of improving midfacial volume loss and/or contour deficiencies.

Subgroup Analyses  
As the study design involved both thin- and thick-skinned subjects, which were either correctly or incorrectly matched to treatment, this created a 4-cohort study. Our results demonstrate that in/correctness of treatment allocation results in differences to the order of the mean ranks between subgroups, in pertinent outcome variables (eg, GAIS, PSQ, MMVS). For example, thin-skinned subjects who incorrectly received a firm product (minimal diffusion and integration), consistently scored the lowest on satisfaction and improvement parameters; while treating thick-skinned individuals with a soft product often required 1.4× more OBT/XpresHAn product than NASHA to maintain similar satisfaction and improvement results as correctly treated thin-skinned subjects. In practice, this resulted in the use of 3 syringes of HA$_L$ versus 4 of HA$_V$. These findings are important in terms of developing a cost-effectiveness model for patients. Moreover, our findings support that in order to ensure the best aesthetic outcomes, injectors should avoid using a hard gel with a high lift capacity, such as HA$_L$ in thin-skinned individuals; as the HA$_L$ group consistently scored the lowest on patient- and physician-assessed scales. Of note, physicians were more critical of results than research subjects, but the subgroup trends in terms of patient satisfaction and physician-rated efficacy were the same.

As the number of injectable products available to physicians increases, evidence in support of their individual performance measures is increasingly necessary. There is growing interest in describing how manufacturing technology can affect the biophysical characteristics of different products and in turn and how these biophysical characteristics affect biomechanical performance. Previous research has revealed how NASHA and OB product integrate differently into the tissues. Apart from the significant differences in the technologies, when plotting the G′ to mean product integration in human skin, researchers found statistically significant correlations. More specifically, they found that products with the lowest G′ have the highest integration score and products with high G′ have the lowest integration scores. Our study contributes to and furthers this research by providing additional information regarding how variable tissue integration can affect clinical outcomes.

Moreover, our findings provide evidence in support of the theory that the unique biophysical characteristics of each filler makes them more appropriate in certain patient populations. For example, aging thin skin lacks projection and volume; and correction of these deficiencies requires larger volumes of soft product. Conversely, aging thick
such as HAV. Ultimately, product choice should depend upon factors such as the degree of correction required in the anatomical area under evaluation, skin quality, soft tissue quality, and quantity.

**Comparison of Subjective and Objective Measures**

In most cases (ie, “70%”), ultrasound validated the results of clinical examination. Therefore, our findings support that clinical examination, consisting of palpation and visualization, can result in moderate accuracy rates for characterizing thin and thick skin types. However, to more accurately measure dermal thickness, objective measures such as ultrasound are required; or perhaps, clinical maneuvers could be standardized to better assess thickness. Regardless of the chosen assessment technique, using these methods enables clinicians to stratify patients in a systematic manner and tailor their treatment regimens by selecting the appropriate product.

A possible reason why clinical examination was not 100% accurate may be due to the difference in dermal thicknesses between the 2 groups. Subjects presenting with thick skin had on average only 0.5-mm thicker skin than those in the thin-skinned group. This is likely too small of a difference to accurately measure using visual assessments alone.

**Strengths**

The premise of and information collected in this trial are easily reproducible, without the need for future investigators to exactly replicate the current study. This is because the hypotheses that thick-skinned patients are better suited to receive HAL and that thin-skinned patients are better suited to receive HAV can be predicted even if future experimental conditions are not identical. Furthermore, during the course of this study, we evaluated the Pinch and Slide Tests. The results of these evaluations revealed that there was reproducibility of the clinical examination and that it does correlate strongly to whether patients are thin or thick skinned. Given the robustness of this data, it will be fully presented in a future publication.

**Limitations**

The findings of this study should be seen in light of a few limitations. For example, a mildly uneven treatment assignment (HAV: n = 17; HAL: n = 13) between the groups and the small sizes of the subgroups limit the statistical power of this trial. However, although the sample sizes were not equal, the means and standard deviations associated with important variables were similar between groups [eg, age, MMVS at baseline, attrition and AE rate, injection volumes]. This suggests that, except for the predictor variable (ie, skin thickness), groups were more alike than dissimilar. Therefore, the unequal sample size should have had little statistical effect. Secondly, various statistical methods are available to accommodate unequal sample sizes. For example, in the calculation of power, we used Hedges’s g instead of Cohen’s d, which provided a measure of the effect size weighted according to the relative size of each sample.

Thirdly, even simple randomization used in randomized controlled trials can produce an unbalanced pattern and; lastly, the validity of trials with unequal randomization ratios are supported by previous research. In addition, our study did not involve a control group, but this was justified on various grounds. When it comes to comparison trials in aesthetic medicine research, it is rare to treat one side of the face while maintaining the contralateral side as a control. This is because recruitment becomes extremely difficult, when using this study design. While control groups are paramount in research, the use of such a group would not have had any validity in the current work. Importantly, using one-of-the-two sides as a control would have had too major issues: (1) Patient recruitment would have been extremely difficult, as subjects would likely not agree to participating in a trial where they would have gone 4 months looking asymmetrical and (2) the likelihood that the research ethics board would reject this study design is high.

There was also a selection bias in that we only investigated the use of the 2 HA products in women. Therefore, our findings may not be generalizable to men who may have other pertinent variables that affect choosing the ideal product. Lastly, the “70% agreement rate between subjective clinical exam and objective ultrasound may be exaggerated for clinicians with less experience than the injector assessed herein.

**CONCLUSIONS**

In this study, we investigated 2 HA products that varied in their levels of efficacy, depending on the characteristics of the subject. As such, each product is best indicated for particular populations. This trial has developed concepts that may be used for the generation of treatment algorithms, such as: the existence of patient strata based on specific
skin characteristics and the possibility of using these strata for the purposes of treatment allocation. It is expected that these concepts may be applied to other families of fillers.

Acknowledgments
Presented at The Canadian Laser and Aesthetic Specialists Society Annual Educational Symposium, Montreal, Quebec, Canada on November 10, 2018.

Disclosures
Dr. Nikolis is a consultant, speaker, and research collaborator for Galderma, Allergan, and Merz Pharma. The other authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

Funding
This study was funded by an unrestricted educational grant from Galderma Canada.

REFERENCES
1. The American Society for Aesthetic Plastic Surgery. Cosmetic Surgery National Data Bank: Statistics 2018. Aesthet Surg J. 2019;39(Suppl_4):1-27.
2. Bray D, Hopkins C, Roberts DN. A review of dermal fillers in facial plastic surgery. Curr Opin Otolaryngol Head Neck Surg. 2010;18(4):295-302.
3. The American Society of Aesthetic Plastic Surgery. Practice Survey 2008. http://www.surgery.org/sites/default/files/2008stats.pdf. Accessed February 19, 2018.
4. Weiss RA, Moradi A, Bank D, et al. Effectiveness and safety of large gel particle hyaluronic acid with lidocaine for correction of midface volume deficit or contour deficiency. Dermatol Surg. 2016;42(6):699-709.
5. Galderma Laboratories, L.P. Restylane® Lyft™ Lidocaine - Instructions for Use; 2014. https://www.restylane.com/sites/g/files/jcdfs206/files/2018-03/Restylane%20LYFT%20Lidocaine.pdf. Accessed June 4, 2018.
6. Galderma Laboratories, L.P. Restylane® Volyme™ Instructions for Use; 2016. https://www.restylane.com/ca/sites/g/files/jcdfs206/files/2018-03/Restylane%20Volyme_90-85520-02.pdf. Accessed June 4, 2018.
7. Goodyear MD, Krieza-Jeric K, Lemmens T. The Declaration of Helsinki. BMJ. 2007;335(7621):624-625.
8. Bhatt A. International Council for Harmonisation E6(R2) addendum: challenges of implementation. Perspect Clin Res. 2017;8(4):162-166.
9. Firooz A, Rajabi-Estarabadi A, Zartab H, Pazhohi N, Fanian F, Janani L. The influence of gender and age on the thickness and echo-density of skin. Skin Res Technol. 2017;23(1):13-20.
10. Darlenski R, Sassning S, Tsankov N, Fluhr JW. Non-invasive in vivo methods for investigation of the skin barrier. Eur J Pharm Biopharm. 2009;72:295-303.
11. Lundgren B, Sandkvist U, Berdier N, Gauthier B. Using a new photo scale to compare product integration of different hyaluronic-based fillers after injection in human ex vivo skin. J Drugs Derm. 2018;17(9):982.
12. Bertucci V, Lin X, Axford-Gatley RA, Theisen MJ, Swift A. Safety and effectiveness of large gel particle hyaluronic acid with lidocaine for correction of midface volume loss. Dermatol Surg. 2013;39(11):1621-1629.
13. Hoffmann K, Stüicker M, Dirschka T, et al. Twenty MHz B-scan sonography for visualization and skin thickness measurement of human skin. J Eur Acad Dermatol Venereol. 1994;3(3):302-313.
14. Pellacani G, Seidenari S. Variations in facial skin thickness and echogenicity with site and age. Acta Derm Venereol. 1999;79(5):366-369.
15. Van Mulder TJ, de Koeijer M, Theeten H, et al. High frequency ultrasound to assess skin thickness in healthy adults. Vaccine. 2017;35(14):1810-1815.
16. Faul F, Erdfelder E, Buchner A, Lang AG. Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. Behav Res Methods. 2009;41(4):1149-1160.
17. Avins AL. Can unequal be more fair? Ethics, subject allocation, and randomised clinical trials. J Med Ethics. 1998;24(6):401-408.
18. Dumville JC, Hahn S, Miles JN, Torgerson DJ. The use of unequal randomisation ratios in clinical trials: a review. Contemp Clin Trials. 2006;27(1):1-12.
19. Akl EA, Briel M, You JJ, et al. Potential impact on estimated treatment effects of information lost to follow-up in randomised controlled trials (LOST-IT): Systematic review. BMJ. 2012;344(2809):1-12.