Comparison of 2.5% agarose gel vs hyaluronic acid filler, for the correction of moderate to severe nasolabial folds

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Abstract
Background: Agarose gel filler is a natural hydrocolloid with a three-dimensional structure similar to the extracellular matrix, with gel formed by hydrogen bonds and electrostatic interactions rather than through chemical cross-linking or polymerization.

Objective: To determine efficacy and safety of 2.5% agarose gel filler for the correction of nasolabial folds.

Methods: In this split-face study, efficacy, safety, and usability of 2.5% agarose gel were compared to those of NASHA-L. Assessments included the nasolabial fold (NLF) Wrinkle Severity Rating Scale (WSRS), Global Aesthetic Improvement Scale (GAIS [blinded investigator]), subject satisfaction, safety (adverse events), and usability.

Results: Sixty-six subjects were treated, and 46/66 (66.7%) were available for evaluation at 3 months, when mean change in WSRS was identical for both products (−1.1 ± 0.4 for 2.5% agarose; −1.1 ± 0.4 for NASHA-L). Scores for each product remained similar across all time points and began to return to baseline between 7 and 8 months. GAIS score followed a similar pattern, rising between months 7 and 8 (2.7 ± 0.6 for 2.5% agarose at month 7-3.3 ± 0.5 at month 8 and 2.7 ± 0.6 for NASHA-L at month 7-3.3 ± 0.5 at month 8). Ultrasound confirmed the longevity of both fillers between 7 and 8 months. All adverse events were transient in nature and resolved within 15 days. Most events were mild in nature, and the number of events was similar between the two fillers.

Conclusion: Treatment with 2.5% agarose gel resulted in improvement that persisted for between 7 and 8 months. The treatment effect was equivalent to NASHA-L.

KEYWORDS
agarose gel, dermal fillers, HA fillers, revolumization, dermal fillers

1 | INTRODUCTION

Revolumization with dermal fillers is one of the primary tools in the nonsurgical armamentarium used in the treatment of facial aging. Revolumization of facial fat pads can correct the "deflated" appearance characteristic of the aging face or be used to fill in fine lines and wrinkles to provide a more youthful appearance. To date, hyaluronic acid (HA) fillers have dominated the injectable filler landscape and represent the entirety of nonbiostimulatory fillers. In spite of their popularity, there remains a need for additional agents that are both safe and can be adapted to a wide range of esthetic filler applications.

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Agarose injectable gel is distinct from all HA fillers in that it is made not from hyaluronic acid, but of D-galactose and 3,6-anhydro-L-galactopyranose sugars (agarose). Agarose is extracted from red algae (Rhodophyta)1 and is a mainstay in molecular biology where it is used as a structural scaffold, as an inert control in a number of assays, in DNA electrophoresis, and as a solidifying agent for bacterial growth media bacteriology plates.2 Agarose becomes a hydrocolloid and when dissolved in water or saline, heated, and allowed to cool, it readily forms a gel. Agarose gel has a three-dimensional structure similar to that of the extracellular matrix. Within this structure, the agarose sugars are held together in a helical formation by hydrogen bonds and electrostatic interactions rather than through chemical cross-linking or polymerization.3,4 The size of the gel pores, matrix density, and gel firmness are dictated by agarose concentration rather than by chemical processes such as the cross-linking required to polymerize hydrated HA particles into gels.2,5 In addition, while HA fillers are degraded by native hyaluronidases, there is no native agarase, and agarose is degraded primarily through the action of macrophages and subsequent degradation by galactosidase.6,7 Given these fundamental differences, the relative performance of these two classes of filler is of particular interest when considering further clinical development and eventual adoption of agarose fillers into clinical practice.

In this year-long study, the efficacy and safety of a 2.5% agarose gel in 0.5% noncrosslinked HA (for lubrication; Algeness™ VL 2.5%, Advanced Aesthetic Technologies, Inc [AAT]) was examined in comparison with NASHA-L (Restylane Perlane™, Nestlé Skin Health SA; marketed as Restylane® Lyft in the United States) for the correction of nasolabial folds (NLF). The study aim was to identify any differences in clinical performance, resorption rate, and device usability.

2 | METHODS

2.1 | Study design

This prospective, single-center, split-face study evaluated the efficacy, safety, and usability of 2.5% agarose gel (Algeness™ VL 2.5%, Advanced Aesthetic Technologies, Inc [AAT]) and (Restylane Perlane™ [NASHA-L, 20 mg/mL] [14-24 mg/mL HA], Nestlé Skin Health SA; marketed as Restylane® Lyft in the United States) for the correction of nasolabial folds (NLF). The study aim was to identify any differences in clinical performance, resorption rate, and device usability.

Subjects were randomized for product injected in the left or right side of the face. Subjects received sufficient product to achieve optimal correction at the first visit and an option for touch-up treatment at 1 month. The study duration was 12 months, with follow-up at week 2 and at months 1, 3, and 4 and then monthly from month 6 to 12. Subjects were followed for 12 months or until the product was shown to resorbed by ultrasound, whichever occurred first. Photographs capturing qualitative changes were taken using a Canfield system at each follow-up time point. Objective and subjective measures were collected as described below.

2.2 | Efficacy measures (WSRS, GAIS, and satisfaction)

The study primary end point was a noninferiority improvement in the NLF based on comparison of investigator-reported WSRS score (range 1 [none] to 5 [extreme] at 3 months; Figure S1). In addition, investigator-reported WSRS scores were collected at months 1, 3, and 4 and monthly from month 6 to 12 or until the subject had completely absorbed the filler. Investigator-reported Global Aesthetic Improvement Scale (GAIS; range 5 [worse] to 1 [very much improved]; Figure S2) was also collected at each follow-up time point for 12 months or until the subject had completely absorbed the filler. At each post-treatment time point until the filler was absorbed, the subject rated their satisfaction with their esthetic results for each side of the face (range 0 [no benefit] to 10 [maximum benefit]).

To evaluate the performance of both fillers, variation in mean WSRS score over the first 3 months was calculated using the Wilcoxon (Mann-Whitney U test) test. Distribution of WSRS and GAIS scores for each filler over time was assessed using a chi-square test. Multivariate analysis (ANOVA) was used to assess correlation between improvement observed and baseline WSRS score.

2.3 | Durability

Treatment durability was assessed with both subjective (GAIS and WSRS) and objective (soft-tissue ultrasound) assessments. Both GAIS and WSRS were used to assess durability based on the time point at which the mean score returned to baseline. Soft-tissue ultrasound was used at each post-treatment visit from month 1 onward. Mean residence time for the injected filler and percent resorption were calculated based on the change from baseline and known volume of filler injected. Difference in mean times of persistence between the two fillers was measured using ultrasound and assessed using Student’s t test.

2.4 | Safety and tolerability

Safety monitoring was carried out for the duration of the study. Subjects were evaluated at both injection visits and each follow-up time point. Subjects were asked to record any adverse events in a
take-home diary for 1 week following injection. Expected injection-related events (pain and discomfort, bruising, swelling, inflammatory reaction, herpes simplex eruption, tenderness, firmness, lumps/bumps, redness, discoloration, itching, and vascular incidents) were included in the diary, and subjects were asked to rate any event as mild, moderate, or severe. Safety and tolerability were assessed using descriptive statistics.

2.5 | Device usability and clinical utility

At the time of initial injection and 1-month touch-up, the injecting investigator rated the clinical usability of each filler based on the handling of each product (1 [bad], 2 [poor] 3 [sufficient], 4 [good], or 5 [excellent]). When selecting their rating, the injector was asked to consider viscosity, extrusion force, smoothness of injection, and lumpiness. The difference between products was assessed using a chi-square test. Clinical utility was assessed using a global efficacy score (0 [no effect] to 10 [maximum effect], for which the evaluating investigator was asked to consider both apparent efficacy and overall tolerability (considering local and injection-related events). Efficacy scores were collected, and any difference between products was assessed using a chi-square test.

3 | RESULTS

3.1 | Study enrollment

Of the 68 enrolled patients, 5 (7.4%) were male and 63 were female (92.6%). The mean age was 38.6 years (range 36-65 years). Two of the enrolled patients withdrew consent prior to treatment. Though the study was open to subjects with an WSRS score of 3-5 (moderate to extreme), only subjects with scores of 3 or 4 (moderate or severe) were enrolled. Of the enrolled patients, 22/68 (32.3%) dropped out; 19/68 (27.9%) were lost to follow-up, 1/68 (1.5%) had a serious adverse event unrelated to the study and withdrew, and 2/68 (2.9%) withdrew consent prior to treatment. Thus, 46/68 (67.6%) completed the study.

The PI of the study transitioned to private practice in the middle of the study, and the shift in study management during this time created delays and variability in the follow-up schedule. There were a significant number of missed visits, but all 68 subjects are included in the safety analysis. Sixty-six subjects were included in the intent-to-treat (ITT) population, and 46 (67.6%) are included in the per protocol (PP) population, as this is the number of subjects who presented at the 3-month post-treatment assessment. For those subjects lost to follow-up, the clinical investigators attempted contact to ensure that they were not withdrawing due to adverse events. To eliminate any potential bias, subjects were randomized to treatment groups where the 2.5% agarose was administered to the left side of the face and NASHA-L administered to the right and vice versa. Of the 66 patients in the ITT population, 51 (77.3%) and 50 (75.8%) subjects were in the 2.5% agarose and NASHA-L groups, respectively. The baseline WSRS was 3, and 15 (22.7%) and 16 (24.4%) subjects in the 2.5% agarose and NASHA-L groups, respectively, had a baseline WSRS score of 4.

3.2 | Treatment

In order to make the best comparison between the two fillers, 0.25 mL of 1% lidocaine was added to 1.4 cc of 2.5% agarose gel filler prior to injection (Restylane Perlane® is formulated with lidocaine). The left and right sides of the face were treated to correction with 2.5% agarose gel or NASHA-L filler using a fanning technique with a needle (with the exception of 1 subject, who was injected using a cannula on both sides). The median volume injected for each product for initial treatment in the ITT population was identical (0.7 cc, range 0.5-1.0 cc per side; Table 1). Five subjects (7.4%) received touch-up treatment at 1 month. There were 3 injections of 2.5% agarose and 3 injections for NASHA-L; 1 subject received an injection on both sides of the face, and the others were touch-ups on 1 side. The median amount injected for 2.5% agarose was 0.5 cc (range 0.4-0.5 cc), and the median amount for NASHA-L was 0.3 cc (range 0.2-0.3 cc). With the exception of 3 intradermal injections (n = 2 for 2.5% agarose and n = 1 for NASHA-L), all injections were subdermal.

3.3 | Investigator WSRS evaluation

At 3 months, 46/66 (66.7%) of subjects (PP population) were available for evaluation. For these subjects, the change in the mean WSRS scores for each treatment at 3 months was identical (−1.1 ± 0.4 for 2.5% agarose and −1.1 ± 0.4 for NASHA-L, difference not statistically significant). The changes in WSRS score for the ITT population were also identical −1.1 ± 0.3 for 2.5% agarose and −1.1 ± 0.4 for NASHA-L (Figure 1). Across all time points, WSRS scores for both fillers were similar and began to return to baseline between 7 and 8 months. At the end of the study (either 12 months or when 2.5% agarose was shown to be absent by ultrasound), WSRS scores had returned to baseline levels. At all time points, the differences between the two treatments in the mean WSRS score remained nonsignificant. Subjects with a baseline score of ≥4 (severe or very severe) had a mean reduction in score.
of 1.5 points, while subjects with a baseline score of 3 (moderate) had a reduction of 1 point on average.

3.4 | Physician GAIS evaluation

At all time points, there was no significant difference observed in PGAIS between the two fillers (Figure 2). Similar to the patterns observed in WSRS scores, mean GAIS score began to rise between months 7 and 8 (2.7 ± 0.6 for 2.5% agarose at month 7-3.3 ± 0.5 at month 8 and 2.7 ± 0.6 for NASHA-L at month 7-3.3 ± 0.5 at month 8). This change corresponded with the first time point for both fillers when there were subjects who were rated as less than improved (GAIS score ≤4). For both 2.5% agarose and NASHA-L, 1 patient’s appearance was rated as unchanged from baseline at month 7. At 8 months, 30.8% of subjects treated with 2.5% agarose and 30.8% of subjects treated with NASHA-L were rated as unchanged from baseline. Of note, at no time point did the physician evaluate a subject as having an appearance as worse than baseline.

3.5 | Subject satisfaction

Across all time points for both fillers, mean subject satisfaction scores remained above 6.0 (Figure 3), indicating that for patients in whom product is still present, satisfaction persists. Any small differences between the fillers were not statistically significant. Mean satisfaction scores for both products peaked around 4 months (9.0 ± 1.7 for 2.5% agarose and 8.5 ± 0.7 for NASHA-L) and slowly declined until month 8, when both GAIS and WSRS scores also reflect diminishing esthetic effect. Past month 9, there was a slight increase in satisfaction, but this may be due to the smaller number of subjects with some amount of unabsorbed filler at these later time points.

3.6 | Treatment durability

In combination with GAIS and WSRS, ultrasound confirmed the longevity of both fillers to be about 8 months. A total of 46/66 (66.7%) of subjects in the ITT population presented for their final study visit. Of these subjects, 27/46 (58.7%) had appeared at the prior visit and been evaluated via ultrasound, thereby allowing the time point of complete product resorption to be assessed. The mean duration of product was 257.5 ± 24.4 days for 2.5% agarose and 258.7 ± 24.5 days for NASHA-L. The difference in persistence was not statistically significant. None of the subjects showed product remaining past 11 months using ultrasound assessment (Figure 4). Representative patient images are shown in Figures 5 and 6, and for the patients shown, 2.5% agarose gel was completely absorbed at 6 and 8 months, respectively.

3.7 | Physician evaluation of product usability and clinical utility

At the first injection and touch-up injection, product usability was measured (scale of 1 [bad] to 5 [excellent]). Mean product handling scores were 3.1 ± 1.0 at the initial injection and 3.5 ± 0.7 at the touch-up injection for 2.5% agarose and 3.1 ± 1.0 at the initial injection and 3.5 ± 0.7 at the touch-up injection for NASHA-L. In the side-by-side investigator evaluations of usability for both products in individual subjects, the scores for each filler were nearly always identical, indicating minimal if any differences in usability. Differences between the two fillers were not statistically significant. Clinical utility was assessed by evaluating investigator satisfaction at both injection time points and at each follow-up visit. Mean satisfaction scores for both products ranged from 6.5 to 8.1 for both products; highest scores were recorded at months 1, 2, and 3. At 3 months, the physician efficacy score was 8.0 ± 0.72 for 2.5% agarose and 8.0 ± 0.75 for NASHA-L. At
9 months, the lowest score for both products was recorded (6.5 ± 0.52 for 2.5% agarose and 6.6 ± 0.65 for NASHA-L). Differences between the two fillers were not statistically significant at any time point.

### 3.8 | Safety and adverse events

A total of 78.4% (n = 54) subjects experienced at least one adverse event on the side treated with 2.5% agarose area compared to 76.5% (n = 52) for NASHA-L. The most commonly reported events were pain, erythema, bruising, redness, edema, and itching. For both fillers, the three most common events were pain (54.5% of subjects for 2.5% agarose and 66.7% of subjects for NASHA-L), erythema (22.7% of subjects for 2.5% agarose and 24.2% of subjects for NASHA-L), and bruising (24.2% of subjects for 2.5% agarose and 28.8% for NASHA-L of subjects). The differences observed were not statistically significant. Adverse events that occurred in > 5% of subjects are shown in Table 2. Nodes (characterized by transient swelling) were reported by 7 (10.6%) of 2.5% agarose-treated subjects and 7 (10.6%) of NASHA-treated subjects. All adverse events were transient in nature and resolved within 15 days. The severity and duration of adverse events were similar for each product. There were no instances of vascular compromise reported. The total number of events was also similar between the two fillers, with 166 events reported for NASHA-L and 151 events reported for 2.5% agarose gel.

### 4 | DISCUSSION

This study shows that over 12 months, 2.5% agarose gel and NASHA-L are equivalent in terms of clinical performance for the correction of NLF. Both WSRS and GAIS scores reflected ongoing improvement and satisfaction until ~8 months (Figures 1 and 2), a pattern supported by subject satisfaction scores (Figure 3), which also began to decline at 8 months. In addition, ultrasound-based evaluation of the injected products showed complete resorption for a majority of subjects at 8 months (Figure 4), with almost no difference between products.

![FIGURE 3](image1.png) Mean Subject satisfaction with treatment over time (score 0-10, with 10 being maximum satisfaction)

![FIGURE 4](image2.png) Time to complete product absorption measured by ultrasound reported by the percentage of subjects at each time point in whom product was shown to be absent

![FIGURE 5](image3.png) A 55-y-old female patient treated on the left side with 0.8 cc of NASHA-L and on the right side with 0.8 CC of 2.5% agarose at baseline (A), month 1 (B), month 3 (C), month 6 (D), and month 8 (E). Complete resporption of 2.5% agarose was noted at month 8.
While these results speak to the similarities between the two products, this study has several significant limitations. First, only 46/68 (67.6%) of subjects completed the study, with the majority of these subjects lost to follow-up (19/68 [27.9%]). Because the PI of the study transitioned to private practice in the middle of the study, the shift in study management during this time created delays and variabilities in follow-up schedule, complicating the analysis. For example, there were only 27 evaluable subjects in whom resorption could be evaluated because 19 subjects were not present at the visit prior to the time point at which complete resorption was shown via ultrasound. In spite of these shortcomings, at the visits where patients were evaluated, the performance of both products was essentially identical, reinforcing the observed similarity between the products in the ITT population. Further, because each subject served as their own control, the drop-out rate did not result in an imbalance in the number of evaluable patients for each product. From a clinician perspective, the usability of and satisfaction with both products was essentially the same, providing important information for future use in the clinical setting. The safety profile of both products was also similar, with both products having similar incidence of AEs of the same nature (Table 2) with no difference in severity and duration. Taken together, these results show that 2.5% agarose is as effective as NASHA-L in the correction of the NLF and is equally well tolerated.

Given the dramatically different composition of the two fillers under study, a similar performance is of interest for a number of reasons. First, agarose is a natural product that does not rely on chemical cross-linking or contain any additional chemicals. The small volume of HA added to the agarose formulation to improve lubrication is noncrosslinked HA, a liquid that is rapidly degraded by native hyaluronidases once injected, usually within 1 day. The rapid breakdown of noncrosslinked HA necessitates modification when HA is to be used as a filler to ensure durable esthetic effect.‡ For HA fillers, longevity and product firmness are achieved most often through use of a 1,4-butanediol diglycidyl ether (BDDE) cross-linker, which remains present in an unreacted form at a concentration of <2 parts per million (ppm), a level considered nontoxic.‡ However, BDDE has been shown to have mutagenic properties,§,∥ and the effect of long-term exposure or exposure from larger volumes of injection remains unexplored. These issues may become increasingly important as nonsurgical body contouring continues to gain popularity and as increased uptake by younger patients increases the lifetime exposure to HA filler. In addition, much larger volumes are generally injected in locations other than the face in clinical settings such as post-traumatic or postsurgical defects, cellulite, or esthetic augmentation. The <2 ppm threshold for BDDE equates to <2.0 μg of BDDE in 1 mL of HA gel and a maximum safe dosage of 20 mL per 60 kg per year.‡ While HA fillers are accepted as safe, a filler that does not rely upon a cross-linking agent would be beneficial. Agarose is an inert substance that is approved for use as a food additive by the FDA.¶ Second, there is always a need for improved

FIGURE 6  A 50-y-old female patient treated on the left side with 0.8 cc of NASHA-L and on the right side with 0.7 CC of 2.5% agarose. The subject is shown at baseline (A-C), month 3 (D-F), and month 6 (G-I). Complete absorption of 2.5% agarose was noted at month 6.
product versatility and safety. While filler injection by a knowledgeable clinician is an inherently safe procedure, reversibility is a central aspect of safety. The action of hyaluronidase on HA is concentration-dependent and requires continuous high doses in order to efficiently act on misplaced filler. While formal testing on agarose filler is needed, theoretically, misplaced agarose gel can be dispersed using saline, and preliminary bench-top experiments with saline and with freshly drawn blood support further investigation. The carrier in agarose gel fillers is either saline (1.5%) or noncrosslinked HA (2.5% [0.4% HA] and 3.5% [0.5% HA]), obviating the need for enzymatic degradation prior to product dilution and dispersion. Finally, because agarose gel qualities are a function of concentration, the material itself is highly adaptable and does not require complex reformulation to generate a range of products that can be adapted to a range of esthetic applications.

Initial approval of agarose gel fillers occurred in 2004 in Europe by the EMA, but early adoption was slow and it was considered primarily as a biocompatible material for reconstructive or regenerative scaffolding. However, with growing esthetic use in the last 5-7 years, the clinical experience of physicians has been positive. Available in concentrations ranging from 1.0% to 3.5%, gel fillers have been used successfully in the NLF, mid-face volumization, temples, jawline, bridge of the nose, and neck. In each area of use, agarose has a safe and predictable effect. This positive clinical experience, in combination with the results presented here, support the use of 2.5% agarose in facial rejuvenation and raise the possibility of future innovations that require larger volumes of product. In combination with clinical performance, the natural origin of agarose and a manufacturing process that does not require the addition of chemicals may make it a preferred filler for both patients and physicians.

| TABLE 2 | Subjects with at least one local AE (in > 5% of subjects) with event frequency and severity |
|---------|------------------------------------------------------------------------------------------------|
| 2.5% Agarose (N = 66) | NASHA-L (N = 66) |
| Occurrence | Median duration (range) | Occurrence | Median duration (range) |
| Pain | | | |
| Mild | 37 | 36 (54.5%) | 30 min (1 min-15 d) | 53 |
| Moderate | 5 | | | 34 |
| Severe | 2 | | | 13 |
| Erythema | | | | |
| Mild | 19 | 15 (22.7%) | 10 min (1 min-3 d) | 20 |
| Moderate | 1 | | | 15 |
| Severe | 3 | | | 2 |
| Bruise | | | | |
| Mild | 16 | 16 (24.2%) | 4 d (60 min-7 d) | 20 |
| Moderate | 6 | | | 8 |
| Severe | 4 | | | 7 |
| Redness | | | | |
| Mild | 18 | 16 (24.2%) | 15 min (1 min-5 d) | 17 |
| Moderate | 1 | | | 11 |
| Severe | 3 | | | 3 |
| Edema | | | | |
| Mild | 16 | 13 (19.7%) | 2 d (10 min-5 d) | 18 |
| Moderate | 7 | | | 6 |
| Severe | 6 | | | 7 |
| Itching | | | | |
| Mild | 11 | 11 (16.7%) | 1 d (30 min-5 d) | 11 |
| Moderate | 9 | | | 7 |
| Severe | 1 | | | 1 |
| Swelling | | | | |
| Mild | 9 | 9 (13.6%) | 2 d (1-5 d) | 7 |
| Moderate | 4 | | | 2 |
| Severe | 4 | | | 5 |

Footnote: Occurrence is the total number of times the adverse event was reported in the study.
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CONFLICT OF INTEREST
Nico Scuderi, Benedetta Fanelli and Pasquale Fino have nothing to disclose. Brian M. Kinney is a shareholder and Board Member of AAT.

DATA AVAILABILITY STATEMENT
Author elects to not share data.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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