# Injection of Stabilized Hyaluronic Acid-Based Gel of Non-Animal Origin for the Correction of Nasolabial Folds: Comparison with and without Lidocaine

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BACKGROUND The use of injectable hyaluronic acid–based gel of non-animal origin, manufactured using the patented NASHA technology, is well established in aesthetic facial procedures.

OBJECTIVE To compare injection pain, dermal filler efficacy, and safety of NASHA-based gel with or without 0.3% lidocaine hydrochloride when administered to the nasolabial fold (NLF).

METHODS Forty-three subjects seeking correction of NLFs, with moderate or severe wrinkle severity, were recruited for this split-face, double-blind, comparative study. NASHA-based gel, with or without lidocaine hydrochloride, was injected into the deep layer of the dermis and/or subcutis, of the NLF. Pain, efficacy, and safety assessments included a treatment preference question, a 100-mm visual analogue scale for pain, the Wrinkle Severity Rating Scale, and adverse event reporting.

RESULTS Ninety percent of subjects (lower 95% confidence limit = 76%) rated injection of NASHA-based gel with lidocaine as less painful than NASHA-based gel alone. Subjects and physicians reported no significant differences in dermal filler efficacy between the two treatments during the 12-month follow-up period. The safety profile was similar for both products.

CONCLUSION NASHA-based gel with lidocaine provides a more comfortable treatment experience than NASHA-based gel alone, with equivalent efficacy and safety observed after 12 months of follow-up.

*Q-Med provided the Restylane Perlane with and without lidocaine and equipment used in this study. Ken Sutor, Fishawack Communications, provided assistance in writing this manuscript.*

In recent years, the demand for nonsurgical facial rejuvenation procedures to enable individual beauty has increased considerably, and augmentation of facial features using injectable filler materials has become one of the most frequently performed aesthetic procedures.[1] The use of hyaluronic acid for nonsurgical procedures in the United States has increased more than 20 times over the past 5 years.[2]

For more than 10 years, Q-Med has used its patented NASHA technology to develop a number of hyaluronic acid-based gels of non-animal origin (NASHA-based gel; Q-Med AB, Uppsala, Sweden). The first injectable NASHA-based gel was Conformité Européene (CE)-marked in Europe in 1996 for the treatment of lips, wrinkles and folds. A number of NASHA-based products have subsequently been developed and extensively studied in the United States, Europe, and Asia. These studies have confirmed the excellent safety and efficacy profile of NASHA-based gel in clinical practice.[3–12] More than 10 million aesthetic treatments have been performed worldwide with NASHA-based gel (Q-Med AB, available at http://www.q-med.com).

NASHA-based gel products provide volume expansion within the dermis and subcutis, smoothing out overlying facial wrinkles and enhancing facial contours, but pain and discomfort can be experienced when the tissue expands; this is associated

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with the total volume administered, the rate of injection, and the injection technique used.[7] A number of pain management procedures can be used to relieve this discomfort, such as topical anesthetic creams, cold therapy, or distraction techniques. An alternative approach is to combine an anesthetic drug with the dermal filler gel. Lidocaine has been successfully combined with injectable collagen fillers since the early 1980s.[13,14] More recently, lidocaine has been incorporated with hyaluronic acid–based dermal fillers available in Europe and the United States.[15–17] Studies have revealed no adverse events (AEs) that were considered to be related to the addition of lidocaine.[9,11]

Q-Med has recently developed a formulation of NASHA-based gel with lidocaine (0.3%) as a constituent to enhance comfort. The objectives of this study were to compare the injection pain, dermal filler efficacy, and safety over 12 months after injection of two formulations of NASHA-based gel (with and without lidocaine) into the nasolabial fold (NLF).

## Methods

This was a randomized, double-blind, split-face, multicenter study conducted in subjects aged 18 and older who were seeking correction of NLFs. Inclusion criteria included a wrinkle severity suitable for treatment with at least 0.5 mL of NASHA-based gel and a Wrinkle Severity Rating Scale (WSRS) score of 3 or 4, with the same wrinkle severity score in both NLFs. Exclusion criteria included active skin disease or inflammation near or on the NLFs; hypersensitivity to hyaluronic acid or local anesthetics; treatment of the NLFs within the last 6 months with nonpermanent fillers, aesthetic facial surgery, laser treatment, or chemical peeling; permanent implant in the NLF area; and reduced sensitivity in the facial region. Participants were also excluded if they had used anticoagulant therapy within 10 days before treatment or antiarrhythmic medication within 1 month before treatment, or had participated in another clinical study within 30 days before inclusion.

One NLF was randomly assigned to receive NASHA-based gel (Restylane Perlane; Q-Med AB) with 0.3% lidocaine hydrochloride; the opposite NLF was treated with NASHA-based gel alone. Both products were injected into the deep layer of the dermis and/or the surface layer of the subcutis of the NLF. Linear threading, fan, or a combination thereof was permissible. The same injection technique was used for both products for each patient to ensure comparability between NLFs. A maximum of 2 mL of NASHA-based gel was administered per NLF, and the site was massaged for conformation with the surrounding tissue. No topical or local anesthesia or other pain-relieving medications were used.

To evaluate the pain of injection separately from the pain of needle insertion, a pause of 3 to 5 seconds was required between insertion of the needle and starting injection. Injection into the second NLF was initiated 15 minutes after the injection into the first NLF to reduce the potential influence of acute pain from the first injection on the pain perception of the second injection. Upon completion of both injections, subjects were asked which of the two treatments was less painful. Using a 100-mm visual analogue scale (VAS), subjects were also asked to assess the pain experienced during treatment and at 5, 15, 30, 60, and 120 minutes after treatment.

Follow-up visits included a telephone contact at 72 hours and a clinic visit at 2 weeks; on both occasions, the question "Since the last visit, has the subject had any signs or symptoms of pain?" was posed. Touch-up treatment was an option 2 weeks after the initial treatment to achieve optimal cosmetic correction (at least 1 grade improvement in WSRS). Thereafter, follow-up visits were scheduled at 3, 6, 9, and 12 months after injection. In addition to pain, safety was assessed using directed questions regarding bruising, redness, swelling, tenderness, and itching (asked immediately after treatment, during the 72-hour telephone call, and at the 2-week visit) and by AE reporting throughout the study (at the end of the treatment visit, during the 72-hour telephone call, and at every post-treatment visit). The subject

**TABLE 1. Wrinkle Severity Rating Scale**

| *Score* | *Description* |
|---|---|
| 5 | **Extreme:** Extremely deep and long fold; detrimental to facial appearance; 2- to 4-mm V-shaped fold when stretched |
| 4 | **Severe:** Very long and deep fold; prominent facial feature; less than 2-mm visible fold when stretched |
| 3 | **Moderate:** Moderately deep folds; clear facial feature visible at normal appearance but not when stretched |
| 2 | **Mild:** Shallow but visible fold with a slight indentation; minor facial feature |
| 1 | **Absent:** No visible fold; continuous skin line |

and treating physician assessed dermal filler efficacy using the WSRS at all clinic visits. WSRS score is based on visual assessment of the length and apparent depth of the NLF without reference to baseline or pretreatment appearance (Table 1).[18] Each WSRS score was illustrated using a photograph of the NLF. Optional retreatment with NASHA-based gel was offered when the WSRS score in both NLFs had returned to the pretreatment value or at the 12-month visit. For an individual subject, administration of such retreatment marked the end of participation in the primary study.

The primary objective of the study was to demonstrate that a two-sided 95% confidence interval of the proportion of subjects choosing NASHA-based gel with lidocaine as the less painful treatment lay above 50%. Assuming a true proportion of 75%, a sample size of 40 was calculated as sufficient (90% power) to reject a proportion of 50% with 95% confidence. The VAS assessments for the two treatments were compared statistically using a paired *t*-test. $P < .05$ was regarded as significant. All efficacy calculations were performed on observed values in the intention-to-treat (ITT) population.

## Results

All 43 study participants were included in the safety population, of whom 42 were included in the ITT population. The 43rd patient was excluded from the ITT population because she was not treated with both study products. The ITT population consisted of predominantly female subjects, with a mean age of 54 (Table 2). All but one subject had the same WSRS score for both NLFs. The average (mean) injection volume for the initial treatment was 1.0 mL for NASHA-based gel with lidocaine and 1.1 mL for NASHA-based gel alone. A combination of fan and linear threading was the most common injection technique; the same injection technique was used for both NLFs in all but one subject (in whom linear threading was used in one NLF and a combination of fan/linear threading was used in the other). Eighteen subjects received a touch-up treatment at the 2-week visit; four subjects received touch-up in only one NLF (NASHA-based gel with lidocaine, $n = 2$; NASHA-based gel alone, $n = 2$). Thirty-five subjects underwent optional retreatment at the end of the study. The mean volume injected was 0.85 mL into NLFs originally treated with NASHA-based gel with lidocaine and 0.86 mL for those originally treated with NASHA-based gel alone.

**TABLE 2. Demographic Data and Baseline Characteristics of the Intention-to-Treat Population**

| *Baseline Characteristic* | n *(%)* |
|---|---|
| Female:male | 40:2 (95:5) |
| Caucasian | 42 (100) |
| Wrinkle Severity Rating Scale score | |
| NASHA-based gel with lidocaine | |
| 3 (moderate) | 28 (66.7) |
| 4 (severe) | 14 (33.3) |
| NASHA-based gel | |
| 3 (moderate) | 27 (64.3) |
| 4 (severe) | 15 (35.7) |
| Prior use of facial fillers or implants | |
| Hyaluronic acid-based therapy | 3 (7.1) |
| None | 39 (92.9) |
| Prior use of other facial dermatological procedures | |
| Yes | 13 (31.0) |
| None | 29 (69.0) |

### *Procedure-Related Pain*

In response to the treatment preference question, 90% of subjects (35/39) rated NASHA-based gel with lidocaine as the less painful of the two

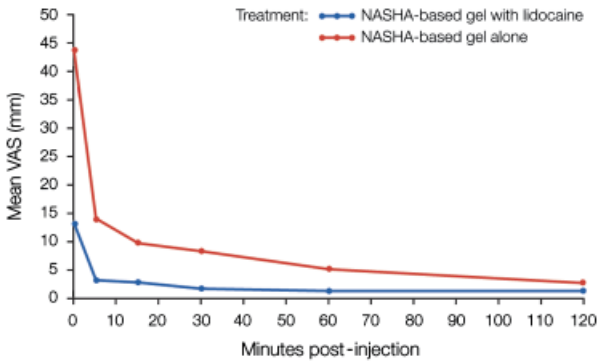


**Figure 1.** Mean pain score on the visual analogue scale (VAS) after injection of NASHA-based gel ($n = 42$).

treatments, with a lower 95% confidence limit of 76%. Three subjects provided no response to the treatment preference question, and because no imputation was made for missing data, they were excluded from the calculation. Three subjects did not distinguish between the two products, and one rated NASHA-based gel alone as the less painful treatment. As assessed on the VAS, injection of NASHA-based gel with lidocaine was significantly less painful than NASHA-based gel alone at all time points during the first 2 hours ($p < .05$; Figure 1).

### *Dermal Filler Efficacy*

Comparison of NLFs treated with NASHA-based gel with and without lidocaine showed similar dermal filler efficacy (Figure 2). At screening, investigators rated both NLFs as equal in 98% of subjects (41/42), compared with 86% (18/21) at 12 months. Of the three subjects with a difference between NLFs at 12 months, two had a lower score (less prominent fold) for the NLF treated with NASHA-based gel with lidocaine, and one had a lower score for the NLF treated with NASHA-based gel alone. In comparison, 93% of subjects (39/42) rated both their NLFs as equal at screening, and 71% (15/21) did so at 12 months. Of the six subjects with a difference at 12 months, four gave a lower score to the NLF treated with NASHA-based gel with lidocaine, and two gave a lower score to the NLF treated with NASHA-based gel alone. There was no statistically significant difference in treatment effect between the two products at any time point (McNemar test).

### *Safety*

The acute and long-term safety profile was similar for the two study products. The most common

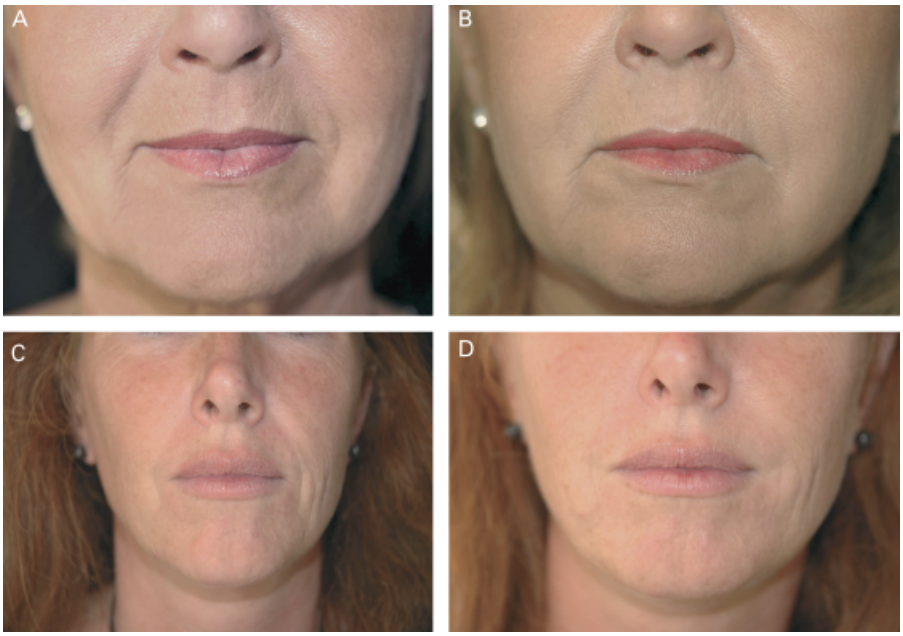


**Figure 2.** Photographs of the nasolabial folds of two subjects taken at baseline (A, C) and 3 months (B, D) after treatment with NASHA-based gel with and without lidocaine.

**TABLE 3. Procedure-Related Reactions Reported After Direct Questioning During the First 2 Weeks After Injection of Hyaluronic Acid-Based Gel of Non-Animal Origin (NASHA-Based Gel) for the Correction of Nasolabial Folds**

| *Procedure-Related Reaction* | *Number of Affected Subjects (Percentage of Safety Population [n = 43])* | |
|---|---|---|
| | *NASHA-Based Gel with Lidocaine* | *NASHA-Based Gel Alone* |
| Swelling | 38 (88%) | 37 (86%) |
| Tenderness | 25 (58%) | 31 (72%) |
| Redness | 26 (60%) | 25 (58%) |
| Bruising | 21 (49%) | 25 (58%) |
| Itching | 11 (26%) | 12 (28%) |
| Pain (not at Day 0) | 8 (19%) | 10 (23%) |
| Subjects affected | 42 (98%) | 41 (95%) |

procedure-related reaction reported in both treatment groups with direct questioning was swelling, followed by tenderness, redness, and bruising (Table 3). These were all anticipated, procedure-related reactions and were mostly of mild intensity. The incidence of pain was comparable for the two study products during the 2 weeks after treatment, reflecting the short duration of action of lidocaine. The number of procedure-related reactions recorded via direct questioning peaked at the 72-hour visit. A few reactions, mainly redness, persisted beyond 2 weeks of follow-up. No unanticipated or serious AEs were reported, and no AEs related to the study product or procedure had late onset (>7 days after treatment).

## Discussion

This study describes the injection pain and 12-month dermal filler efficacy and safety of NASHA-based gel for the correction of NLFs with and without lidocaine. The incorporation of lidocaine with NASHA-based gel provides a new pain-relieving alternative for individuals considering facial augmentation. Accordingly, the majority of participants in the current study considered the injection of lidocaine-containing NASHA-based gel to be a more comfortable injection experience than NASHA-based gel alone.

One of the main barriers to cosmetic treatment is pain at the injection site. Provision of adequate anesthesia will hopefully reduce any apprehension associated with the procedure and thereby encourage new interest in facial augmentation. A more comfortable injection experience should also improve satisfaction among NASHA-based gel recipients, who may then be more likely to return for retreatment.

Although NASHA-based gel is biocompatible, facilitating an excellent safety profile, it is also biodegradable.[19] The new NASHA-based gel containing lidocaine has the same chemical and physical characteristics (gel content, particle size, pH, and degree of modification) as NASHA-based gel without lidocaine. Lidocaine hydrochloride is easily dissolved in NASHA-based gel, leaving the hyaluronic acid concentration of 20 mg/mL unchanged. Lidocaine has also been shown to be homogeneously distributed within the NASHA-based gel. In vitro studies have revealed that the drug release is diffusion controlled and that the majority of the lidocaine (80%) is released within 2 hours (Q-Med AB, unpublished data). This means that the lidocaine is not bound to the gel but is free to yield the desired anesthetic effect.

Although the addition of lidocaine does not affect the properties of NASHA-based gel, it is important to consider whether the breakdown of NASHA-based gel may be affected in vivo. In the current study, the addition of lidocaine did not impair the visual improvement up to 12 months after NASHA-based gel treatment, indicating that durability is not affected. The effect of NASHA-based gel was recently shown to persist for up to 18 months in NLFs with only one retreatment.[12] An improvement of at least one WSRS grade was observed in almost all patients (97%).

NASHA-based gel was well tolerated in the present study, with no serious or unanticipated AEs reported during the 12-month follow-up. These results are

compatible with previous clinical experience in the context of facial aesthetic procedures. The AE profile of the two treatments was also similar, indicating that addition of lidocaine has little or no effect in this regard. No systemic treatment-related AEs were observed in the current study. Lidocaine has a relatively benign safety profile, with low numbers of AEs reported with its use. Lidocaine-related AEs are generally dose related and result from high plasma levels,[20,21] which are unlikely to occur in this setting. True hypersensitivity reactions to lidocaine are considered to be rare.[22,23] Although there are some reports of allergic reactions to lidocaine, these have been mainly linked to the use of preservatives.[23,24] A preservative-free formulation of lidocaine is used in the current formulation of NASHA-based gel, and therefore allergic reactions to this formulation are highly unlikely.

The combination of lidocaine with dermal fillers, unlike topical anesthetic creams, does not alleviate pain associated with needle insertion. However, a recent study indicates that pre-incorporation of lidocaine in the formulation may alone provide adequate pain relief[15]; there was little difference in comfort levels between subjects who had topical anesthesia cream applied before the injection and those who did not. It is ultimately a matter of the individual's pain perception as to whether the pain associated with needle insertion is acceptable or if additional (topical) anesthesia is required.

The split-face design of the present study was chosen so that each subject could serve as their own control and the variability in pain perception between subjects could not confound comparison of the two treatments. The second injection was delayed after the first by 15 minutes in order to minimize any carry-over effect of pain from the first injection to the second injection. Although carry-over effects cannot be eliminated, the randomized order in which treatments were administered should maintain integrity of the results.

In conclusion, we have demonstrated that the combination of NASHA-based gel and lidocaine provides a more comfortable treatment procedure for individuals seeking correction of NLFs than injection of NASHA-based gel alone. Furthermore, the current study indicates that the inclusion of lidocaine has little or no effect on the acute or long-term safety or dermal filler efficacy of NASHA-based gels.

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