Patient Comfort, Safety, and Effectiveness of Resilient Hyaluronic Acid Fillers Formulated With Different Local Anesthetics

Joely Kaufman-Janette, MD, † John H. Joseph, MD, † Stephen H. Dayan, MD, † Stacy Smith, MD, ‡ Laura Eaton, MSN, APRN, FNP, || and Pauline Maffert, MSc¶

BACKGROUND Maximizing patient comfort during hyaluronic acid gel injection is a common concern that is usually addressed by selecting fillers with lidocaine.

OBJECTIVE Two randomized, double-blinded, split-face trials aimed to demonstrate noninferiority of specific hyaluronic acid fillers incorporating mepivacaine (RHA-M) versus their lidocaine controls, at providing pain relief.

METHODS Thirty subjects per trial received injections of RHA1-M versus RHA1, and RHA4-M versus RHA4, respectively, in the perioral rhytids (PR) and nasolabial folds (NLF). Pain was assessed on a visual analog scale; aesthetic effectiveness was evaluated with validated scales, and safety was monitored based on common treatment responses (CTRs) and adverse events (AEs).

RESULTS RHA-M fillers proved as effective as their lidocaine counterparts at reducing pain (noninferior, \( p < 0.0002 \) and \( p < 0.0001 \)). Bilateral wrinkle improvement was measured both in the PR (\( -1.5 \pm 0.6 \) points on each side) and in the NLF (\( -1.8 \pm 0.6 \) and \( -1.9 \pm 0.5 \) points) trials at one month, with virtually identical responder rates (\( \geq 96.7 \% \)). Common treatment responses and AEs were similar between treated sides, and none was clinically significant.

CONCLUSION Resilient hyaluronic acid fillers with either mepivacaine or lidocaine are equally effective at reducing pain during treatment and equally performant and safe for correction of dynamic facial wrinkles and folds.

While hyaluronic acid (HA) fillers have proven to be generally safe and effective in a wide range of aesthetic indications, pain and discomfort are common complaints of patients requiring cosmetic procedures involving dermal fillers.¹

Topical, local anesthesia, and cooling systems have been employed with some success, yet, in some areas, and some patients, these are not adequate. Topical anesthesia is often insufficient at eliminating pain and requires an extended time to onset. Local anesthesia adequately controls pain but can distort the area, making it more challenging to determine treatment outcome.²

Several comparative trials demonstrated that fillers incorporating lidocaine enhance treatment comfort and optimize the injection experience while maintaining a similar safety and effectiveness profile to their counterparts without lidocaine. Most of these trials evaluated the outcomes of split-face filler injection into the nasolabial folds (NLF), administering the lidocaine-containing version on one side of the face and the lidocaine-free version on the other side. Throughout all studies, injection site reactions and adverse events (AEs) occurred at comparable rates, while product efficacy measured on aesthetic scales was the same. Lidocaine adjunction only impacted injection site pain, based on subject self-reporting on visual analog scales (VAS), which confirmed that pain was systematically reduced on the side injected with lidocaine-containing gels.³–⁸

As a result, most commercially available HA fillers now incorporate lidocaine in their formulation, whereas the possibility of using alternative anesthetic agents has been poorly explored.

Mepivacaine is a well-known anesthetic drug available both in Europe and in the United States.⁹,¹⁰ As with lidocaine, mepivacaine has been commonly used as a local anesthetic (infiltration and regional nerve block) for nearly 60 years. Both molecules are local anesthetics from the amide family with similar physicochemical properties and identical metabolism pathway.¹¹–¹⁴
Clinically, mepivacaine has a fast onset, similar to that of lidocaine (11–12 minutes), but a slightly longer half-life (114 vs 96 minutes15) due to the lack of vasodilator activity.16 Reducing vasodilating activity may represent an additional safety factor for mepivacaine; it helps keep systemic levels low and may limit bruising.17

The range of Resilient Hyaluronic Acid (RHA) fillers was developed to meet various clinical needs while respecting facial dynamics. It comprises several formulations with integrated lidocaine, each possessing unique rheological properties dedicated to treat specific indications. Considering the similarities between lidocaine and mepivacaine, replacing the anesthetic agent was hypothesized to provide comparable pain relief in a given indication.

Objectives
Two clinical trials were conducted to investigate whether RHA fillers with mepivacaine (RHAR-M and RHA4-M) were noninferior to RHA fillers with lidocaine (RHAR and RHA4) in terms of reducing injection site pain and to explore the overall safety and effectiveness of both treatments in previously validated indications, namely, NLF and peri-orbital rhytids (PR).

Materials and Methods

Trial Design and Population
These randomized, double-blinded, within-subject, controlled, multicenter, FDA-regulated, prospective, clinical trials were conducted following the International Conference on Harmonization, Good Clinical Practice guidelines, Code of Federal Regulations, and the Declaration of Helsinki. Both studies received approval from an institutional review board and were registered and posted on ClinicalTrials.gov (NCT04069585 and NCT04087395). All subjects gave informed consent before any study procedure being performed.

The target population for inclusion was adults of 22 years or older, with moderate-to-severe bilateral wrinkles in the studied indications, that is, PR in the RHAR-M study, safety evaluations also included lip and NLF in the RH4-M versus RHA4 study.

Subjects who met all inclusion criteria and no exclusion criteria received injections of the RHA-M filler in one side of their face and of the RHA control filler (with lidocaine) in the other side. The side injected first was randomized as well as the product assignment. Both treating investigators (TI) and subjects were blinded to the treatment. Additional use of anesthetic agents (e.g., EMLA, dental blocks, ice, etc.) was prohibited.

Anesthetic effectiveness, as well as safety and aesthetic effectiveness end points, were assessed separately on each side of the mouth or face, and subjects were followed up to one month after treatment.

Treatment
RHA Redensity (RHAR) and RHA4 (TEOXANE S.A. Geneva, Switzerland) are dermal fillers composed of BDDE cross-linked HA and 0.3% lidocaine hydrochloride in a physiological phosphate buffer (pH 7.3). Both gels are manufactured using the RHA technology to reduce the modification degree (MoD) of HA in the final product. RHAR is formulated with 15 mg/mL of high-molecular-weight, lightly cross-linked HA (MoD = 2%), whereas RHA4 contains 23 mg/mL of more highly crosslinked HA (MoD = 4%). RHAR-M and RHA4-M present the same physicochemical specifications as their respective controls but incorporate 0.3% mepivacaine hydrochloride instead of lidocaine.

In the RHAR-M study, two upper and two lower quadrants were defined above the upper lip and below the lower lip for treating PR. Injections were not permitted in an 8-mm “no-treatment” zone located between the left and right quadrants to avoid mix-ups during evaluation due to anesthetic diffusion. Subjects first received injections in the upper quadrants—used for the primary end point evaluation—before being treated in the lower quadrants using the same device (RHAR or RHAR-M) as for the upper quadrant of that side. All injections were performed in the dermis, with the 30 G by ½” needle supplied in the packaging.

In the RHA4-M study, subjects received injections of RHA 4 and RHA4-M into the left or right NLF using the provided 27 G by ½” needle. Injection depth ranged from the deep dermis to the superficial subcutaneous tissue. Investigators were required to use the same injection technique on both sides of the face.

Study End points and Variables

Anesthetic Effectiveness End points

The primary end point was the injection site pain felt during the injection, as assessed by the subject on a 100-mm VAS, immediately after injection in each upper perioral quadrant (RHAR-M study) or each NLF (RHA4-M study). Injection site pain in each side of the face was also assessed at 15, 30, 45, and 60 minutes after the injection. The duration of anesthetic effect was estimated based on subject self-assessment performed every hour until return to normal sensation.

Safety End points

Subjects recorded the nature, severity, and duration of any reaction occurring in each side of their face in a 30-day common treatment responses (CTR) diary. In addition to CTR diaries, AEs were monitored throughout the study. In the RHAR-M study, safety evaluations also included lip functionality assessments performed at Visit 1 (pre- and postinjection) and Visit 2 (30 days after treatment).

Aesthetic Effectiveness End points

Aesthetic effectiveness end points included TI assessments on Teoxane proprietary, validated, 4-point PR severity rating scale (PR-SRS) or 3-point NLF wrinkle severity rating scale (NLF-W5RS), which were performed at Visit 1 (pre- and postinjection) and Visit 2 (30 days after injection).

Treatment effectiveness was also evaluated by both the TI and the patient on the Global Aesthetic Improvement
Scale (GAIS), a 5-point, nonvalidated comparative scale ranging from “much improved” (Grade 1) to “much worse” (Grade 5). Patient-reported outcomes included the PR or NLF domain of the FACE-Q and a subjective satisfaction questionnaire.

**Statistical Analysis**

For both studies, noninferiority was to be demonstrated if the injection site pain during injection of RHA-M filler was statistically noninferior to the injection site pain felt during injection of RHA filler, considering a 10-mm noninferiority margin. The primary end point was analyzed using a one-sided paired t-test, with a 5% significance threshold.

Secondary end points were analyzed using paired two-sided tests, parametric or nonparametric (two-sided Wilcoxon signed rank test), as appropriate. All statistical analyses were performed using SAS (statistical analysis software) 9.4 (SAS Institute Inc., Cary, NC).

**Results**

**Study Population**

Thirty subjects per study were enrolled at three investigational sites in the United States. The mean age in RHAR-M and RHA4-M studies was 64.3 ± 8.2 and 57.0 ± 9.7 years, respectively. Most subjects were women, reaching 100% in the RHAR-M study. Darker skin phototypes accounted for 23.3% and 36.7% of the study populations (See Supplemental Digital Content, Table S1, http://links.lww.com/DSS/B112).

**Injection Volume and Technique**

Study and control devices were injected into the allocated side of the face or mouth, using the same injection technique bilaterally. Injected volumes were nearly identical for RHA and RHA-M fillers (Table 1). Approximately 0.4 mL of RHAR/RHAR-M was required to treat vertical PR above and below half of the mouth, whereas 1.1 mL of RHA4/ RHA4-M was used for correcting each NLF.

**Anesthetic Effectiveness End points**

Subjects assessed pain during injection of each upper PR quadrant in the RHAR-M study and during injection of each NLF in the RHA4-M study (Figure 1). This subject pain assessment was taken immediately on completion of the injected side. The average pain differences (RHAR – RHAR-M; RHA4 – RHA4-M) between the two injected sides were −2.6 ± 10.3 and −0.8 ± 8.1 on the 100 mm VAS, respectively. Noninferiority (δ = 10 mm) was therefore achieved in both trials (p < .0002 for RHAR; p < .0001 for RHA4).

Injection site pain promptly decreased in both sides of the mouth or face, averaging 6.3 versus 6.8 mm in the perioral lines 15 minutes after RHAR versus RHAR-M treatment and 5.1 versus 4.9 mm in the NLF 15 minutes after RHA4 versus RHA4-M treatment. Pain had virtually disappeared one hour after the injection (See Supplemental Digital Content, Figure S1, http://links.lww.com/DSS/B111). Pain levels were not significantly different between the two injected sides at any time point (p > .5).

The duration of anesthetic effect was also similar between treatment groups (p = .1460 and p = .1467). Half of the population returned to a normal sensation after less than 3 hours; however, there was a skewed data distribution due to subjects deemed outliers who still reported anesthetic effects after 10 hours (See Supplemental Digital Content, Figure S2, http://links.lww.com/DSS/B111). Although not statistically significant, the aesthetic sensation was somewhat longer on the RHA-M injected side.

**TABLE 1. Injection Volumes and Techniques**

| RHA1-M Study: Perioral Rhytids Treatment (N = 30) | RHA4-M Study: Nasolabial Folds Treatment (N = 30) |
|-----------------------------------------------|-----------------------------------------------|
| **Injection Volumes per Side**                | **Injection Volumes per Side**                |
| Perioral Quadrant                             | Perioral Quadrant                             |
| RHA1                                         | RHA1-M                                       |
| Upper                                        | Upper                                        |
| 0.27 ± 0.08                                  | 0.27 ± 0.09                                  |
| p = .8325*                                   | p = .8325*                                   |
| Lower                                        | Lower                                        |
| 0.22 ± 0.10                                  | 0.23 ± 0.13                                  |
| p = .9570*                                   | p = .9570*                                   |
| Upper + lower                                | Upper + lower                                |
| 0.40 ± 0.16                                  | 0.41 ± 0.19                                  |
| p = .3817*                                   | p = .3817*                                   |

**Injection techniques**

- Fan like (N = 10, 33.3%)
- Linear threading (N = 10, 33.3%)
- Linear threading, multiple, punctuate pools (N = 10, 33.3%)
- Linear threading, fan like (N = 1, 3.3%)

* Following Kolmogorov–Smirnov test for normality, p values were obtained from two-sided Wilcoxon signed-rank tests.
sides, disappearing in average $3.6 \pm 3.6$ hours after PR treatment and $6.0 \pm 5.9$ hours after NLF treatment, as compared with $3.0 \pm 2.1$ hours and $4.1 \pm 4.5$ hours on the lidocaine control side.

**Aesthetic Effectiveness End points**

RHA and RHA-M filler treatments provided identical aesthetic improvements in the two studied indications. Baseline severity of subjects’ PR was markedly reduced, as assessed on the PR-SRS both immediately after the injection and at day 30 (Figure 2). The average severity score for each side decreased similarly by $1.5 \pm 0.6$ post-injection and $1.4 \pm 0.6$ after one month ($p = 1.000$). This corresponded to bilateral responder rates (proportion of subjects showing at least a 1-point improvement on the PR-SRS) of 96.7% at one month.

Similarly, RHA4 and RHA4-M treatments led to a 1.8-point decrease on the NLF-WSRS post injection (Figure 2). Absolute score differences were also nearly identical after one month, averaging $1.8 \pm 0.6$ and $1.9 \pm 0.5$ in each treatment group ($p = .2188$), corresponding to responder rates of 96.7% and 100%.

All (100%) patients enrolled in the two studies were deemed improved or much improved on both sides of the mouth or face, according to GAI scores provided by both the TI and the subject, postinjection and at day 30. Assessment of patient-reported outcomes with the FACE-Q showed substantial, nearly identical improvement at one month, reaching $73.9 \pm 28.9$ and $77.2 \pm 25.8$ points on the PR domain for RHAR-treated and RHAR-M-treated sides, and $88.5 \pm 16.2$ and $89.9 \pm 15.2$ points on the NLF domain for RHA4-treated and RHA4-M-treated NLF, respectively (See Supplemental Digital Content, Figure S3, http://links.lww.com/DSS/B111). In both studies, 96.7% of patients reported being satisfied with their treatment on both sides of the mouth or face one month after the injection.

**Safety End points**

The proportion of subjects experiencing at least one CTR (e.g., redness, swelling, bruising, etc.) of each category was similar between treatment groups, with the majority of CTRs resolving in 14 days or less. Treatment groups were also similar regarding CTR severity. Most of these reactions were deemed mild or moderate by the subject. All CTRs that
were persistent on the last diary day ended up being mild as per investigator’s evaluation.

All treatment-related AE (TRAE) originated from CTR diaries, with 9 CTRs from 4 (13.3%) subjects and 11 CTRs from 5 (16.7%) subjects being reported as AEs in patients treated for PR and NLF, respectively. The majority of these TRAE were injection site induration, originating from firmness CTR. The rationale for elevating CTR to an AE if the CTR was present on the last diary day (day 30) or if it was manually entered in the “other” category of the diary. A majority of subjects who experienced TRAEs reported identical reactions for both injected sides (See Supplemental Digital Content, Table S2, http://links.lww.com/DSS/B112), all of which resolved spontaneously within days or weeks.

In the RHAR-M study, assessments of lip functionality (lip movement, lip sensation, and lip function) were unchanged after treatment of the PR, regardless of the injected device. There were no serious TRAEs, unanticipated device-related events, nodular complications, or vascular compromise events.

Discussion
To the best of the authors’ knowledge, this is the first publication reporting the results of randomized, controlled trials comparing the safety and effectiveness of HA fillers formulated with two different local anesthetics.

The evaluation of anesthetic effectiveness, aesthetic improvement, and overall safety of RHA Mepivacaine treatment was performed in two distinct aesthetic indications, allowing to consider variable treatment parameters, such as filler rheological properties, area, needle size, and depth of injection.

The primary objective was achieved, as RHAR-M was shown to be noninferior to RHAR, and RHA4-M was noninferior to RHA4, in terms of reducing injection site pain in their respective indications. Overall, study injections were well-tolerated with average pain levels approximating those reported in the literature and decreasing to a minimal intensity at the end of the consultation. Subjects responded similarly to mepivacaine and lidocaine, with anesthetic effects disappearing in a few hours. Although not significant, the average duration of local anesthesia was slightly higher in RHA-M groups, possibly due to the reduced vasodilating activity, thereby leading to prolonged body clearance of mepivacaine.

Mepivacaine did not adversely change the devices’ safety profile, as RHA and RHA-M injections resulted in similar rates of common treatment reactions, which were all transient and resolved without treatment. A majority of TRAEs occurred bilaterally and hence were unrelated to the anesthetic agent.

Importantly, changing the anesthetic agent also did not affect the overall performance of study treatments, which provided drastic improvement in the treated areas, as shown by the decrease of bilateral wrinkles severity scores, and further confirmed by high rates of patient satisfaction. Aesthetic outcomes obtained in this study corroborate data from previously published trials demonstrating the long-term effectiveness of RHA fillers formulated with lidocaine.

In a 64-week study, more than 89% of subjects treated with RHA4 maintained at least a 1-grade improvement on the NLF-WSRS at the last follow-up visit, whereas in a 52-week study, 66% of subjects injected with RHAR into their PR were still responders on the PR-SRS, one year after treatment. As both lidocaine and mepivacaine are promptly metabolized once injected in the body (with estimated in-vivo half-lives of 1 to 2 hours), changing the anesthetic agent is unlikely to have any impact on product durability.

Conclusion
In these two, prospective, randomized, split-face, controlled trials of 30 subjects, RHA fillers formulated with mepivacaine were shown to be noninferior to their respective lidocaine controls in terms of injection site pain reduction. Regardless of the anesthetic agent, RHAR and RHA4 showed an excellent effectiveness and safety profile for the treatment of dynamic wrinkles and folds as per their respective indications while ensuring patient comfort and minimal injection pain.

The range of RHA fillers provides an aesthetic toolbox of HA fillers adapting to facial dynamic, from superficially implanted gels adapted to treat fine lines such as PR to volumizing products developed for the correction of deep wrinkles and volume loss.

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