Preliminary Report

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A Blinded, Randomized, Split-Face Pilot Study of Bruising and Pain With Hyaluronic Acid for Correction of Perioral Lines Using No Lidocaine, Lidocaine Alone, and Lidocaine and Epinephrine

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Abstract

Background: Hyaluronic acid (HA) fillers are sometimes mixed with lidocaine to mitigate pain. Whether the addition of epinephrine to lidocaine provides greater benefits in bruising and pain has not been fully reported.

Objectives: The investigators explored the severity of bruising and pain in patients treated with the cohesive polydensified matrix HA (CPMHA) in 3 different preparations: CPMHA (Belotero Balance [BEL]), CPMHA with lidocaine (BEL-L), and CPMHA with lidocaine and epinephrine (BEL-LE).

Methods: In a blinded, split-face, 14-day study, 30 patients were divided into groups of 10. One group received 1.0 mL BEL in the perioral lines on 1 side and 1.0 mL of BEL-LE on the other side. A second group received 1.0 mL of BEL on 1 side and 1.0 mL of BEL-L on the other side. The third group received 1.0 mL of BEL-L on 1 side and 1.0 mL of BEL-LE on the other side. Over 3 visits, the treating investigator, the patients, and a blinded investigator rated the bruising.

Results: Bruising occurred in each treatment group by day 1 but resolved for half of the patients by day 7 and for all patients by day 14. Split-face comparison did not reveal a significant difference in pain and bruising scores among the 3 preparations.

Conclusions: No significant difference was found in bruising or pain in patients treated with BEL, BEL-L, and BEL-LE. Studies with a considerably larger sample size are warranted to determine statistically significant and clinically meaningful differences between and among the various formulations.

Level of Evidence: 3

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Facial volume loss is one of the effects of the natural aging process. Facial fillers have become more common as the number of safe injectable products has increased. These products range from autologous fat to calcium hydroxylapatite to hyaluronic acids and are used on different cosmetic areas.[1-3] In the lower part of the face, volume loss may present as nasolabial folds (NLFs), perioral lip lines (rhytids), oral commissures, and marionette lines. Wrinkles are the visible effects of dermal creasing caused by loss of volume and by repeated facial movement and expression combined with dermal elastosis.[4] The wrinkles are typically perpendicular to the direction of the underlying facial muscles.[5] The cohesive polydensified matrix hyaluronic acid (CPMHA) Belotero Balance (BEL; Merz North America, Inc, Greensboro, NC) is indicated for injection into the mid-to-deep dermis for

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correction of moderate-to-severe facial wrinkles and folds, such as NLFs.[6] Prior studies have confirmed the safety and effectiveness of BEL in treating NLFs, oral commissures, and other areas of the face.[7-12]

In 2007, an article was published citing a novel way of mixing the soft-tissue filler calcium hydroxylapatite (CaHA) with lidocaine to reduce pain during injection of the hand.[13] In 2009, the Food and Drug Administration (FDA) sanctioned mixing lidocaine with CaHA.[14,15] Physicians quickly surmised that lidocaine with CaHA to mitigate pain could perhaps be extended to the addition of lidocaine to hyaluronic acids (HA).[16-18]

Lidocaine acts primarily by inhibiting sodium influx through sodium-specific ion channels in the neuronal cell membrane (specifically named the voltage-gated sodium channels). The receptor site for the lidocaine is believed to be located at the cytoplasmic (inner) portion of the sodium channels. Lidocaine passes through the cell membrane readily in its nonionized form. Once it enters the cell membrane it becomes ionized by becoming protonated and attaches to the receptor on the sodium ion channels. When the influx of sodium is interrupted, an action potential cannot arise, and signal conduction is inhibited. The receptor site is thought to be located at the cytoplasmic (inner) portion of the sodium channel.

Once inside the cell, the local anesthetic is in equilibrium with the formation of the protonated (ionized) form, which does not readily pass back out of the cell. This is referred to as "ion-trapping." In the protonated form, the molecule binds to the local anesthetic binding site on the inside of the ion channel near the cytoplasmic end. Most local anesthetics work on the internal surface of the membrane, ie, the drug has to penetrate the cell membrane, an action best achieved in the nonionized form.[19-23] In clinical practice, many physicians are now mixing HA with lidocaine—with or without epinephrine (for vasoconstriction)—to mitigate bruising.[24-26]

We were interested in the effect that different preparations of BEL would have on severity of bruising. We were also interested in severity of pain, comparing lidocaine alone to lidocaine/epinephrine preparations. Thirty patients were enrolled in our study to evaluate the severity of pain and bruising with 3 different mixing preparations: 1 with BEL; 1 with BEL and lidocaine; and 1 with BEL, lidocaine, and epinephrine. Split-face comparisons were used to eliminate the confounding effect of inter-patient pain sensitivity and bruising. Therefore the pain and bruising on one side of the lip was compared to the contralateral side in the same patient.

In this blinded, split-face study, we sought to assess severities of bruising and pain across 14 days in 3 different mixing protocol preparations: BEL alone (BEL), BEL with lidocaine (BEL-L), and BEL with lidocaine and epinephrine (BEL-LE).

METHODS

Beginning with screening and enrollment in July 2013 and completing analysis in November 2013, this was a randomized, blinded, and split-face study of 30 patients from 1 United States (US) investigational center. The study was conducted in accordance with the guidelines set forth in the Declaration of Helsinki. Patients underwent superficial to mid-dermal injection of 3 different mixing preparations of BEL (BEL, BEL-L, and BEL-LE) for correction of lip wrinkles.

Study Population

Inclusion Criteria

Individuals were eligible for inclusion in the study if they were men or nonpregnant, nonbreastfeeding women, 18 to 75 years of age, and seeking treatment for correction of perioral lines. Those eligible manifested pretreatment perioral line severity of mild to severe using the validated Merz wrinkle-severity scale of lips at rest.[8] Patients had the ability to understand and comply with the requirements of the study, were willing to abstain from exclusionary procedures for the duration of the study, were willing to give written informed consent to participate in the study, and (women only) were willing to use an acceptable form of birth control throughout the study.

Exclusion Criteria

Patients who were not eligible for the study were associated with one or more of the following conditions: active or chronic skin disease, inflammation or related conditions in the perioral area, recent procedures based on active dermal response (eg, laser or chemical peeling procedures) on the perioral area within 4 weeks prior to study treatment, anticoagulant therapy, previously experienced unanticipated adverse effects when treated with HA products, severe allergies manifested by a history of anaphylaxis or a history or presence of multiple severe allergies, a history of allergies to gram-positive bacterial proteins, any condition which—in the opinion of the investigator—made the patient unsuitable for inclusion, cancerous or precancerous lesions in the area to be treated, and participation in any interventional clinical trial within 30 days prior to treatment.

Screening

Screening and treatment were performed at the first visit. Following study approval by the institutional review board (Aspire IRB, Santee, California), 30 women were screened; they were then counseled on the risks and benefits of the procedure. Screening included recording of medical history, obtaining informed consent, and assessing eligibility criteria. After informed consent was obtained, the patients were enrolled.

At screening, the investigator and the patients used a validated Merz 5-point Wrinkle Severity Scale of lip lines at rest to evaluate the visual appearance of the Lip Wrinkle lines independently for study inclusion.[8] At rest Scale Scores had to range from mild (1) to severe (3) for the selected lip lines to be eligible for enrollment. Standard photographs (facing frontally) were taken to document pretreatment condition using a Canfield Camera (Canfield Clinical Services, Passaic, NJ: Canon EF-S 60 mm f2.8 macro lens, with a face device zido cart and chin rest).

Treatment

Treatment was administered via 30-G needle at baseline (day 0) for optimal correction of lip wrinkles, defined as the best aesthetic result that could be obtained for the lip line of an individual study participant using 1 mL of filler per side. One mL was used on each side for a total of 2 mL across all patients. To help keep the study as blinded as possible, all syringes were premixed by the clinical research coordinator in a location removed from the treatment area. In addition, syringes were blinded at the time of injection, with an assistant overseeing the procedure to make certain that the appropriate mixtures for each patient were provided to the investigator during the time of injection. The BEL syringe (without any concentration of lidocaine or lidocaine epinephrine) was similarly transferred back and forth 20 times using an empty syringe in order to look comparable to the BEL-L and BEL-LE syringes.

The volumes in each of the syringes were adjusted to 1 mL in total. The BEL syringe consisted solely of 1.0 mL of hyaluronic acid; the BEL-L consisted of 0.3 mL of lidocaine HCL 1% added to BEL; and the BEL-LE syringe consisted of 0.3 mL of lidocaine HCL 1% and epinephrine 1:100,000 added to BEL (Hospira, Inc., Lake Forest, IL). The syringes were marked with "L" for left and "R" for right, based on preinjection randomization. All injections were performed in the superficial dermis with serial punctures and linear threading techniques. The entire 1-mL syringe of 1 mixture was injected on 1 side of the upper and lower lip followed by injection of 1 mL of a different mixture on the contralateral side. Consequently, each patient was injected with a total of 2 mL of product, 1 mL on each side. The volume of lidocaine was 3 mg in the BEL-L syringes, and 3 mg, along with 3 mcg of epinephrine, in the BEL-LE syringes.

As part of the randomization process, sealed envelopes with equal numbers of the treatment arms were prepared prior to recruitment. A staff member, independent of treatment and recruitment, shuffled the envelopes. The envelopes were kept in a locked cabinet and the envelope on top was opened only after a patient qualified for enrollment. Three cohorts, each composed of 10 patients, were randomly assigned to receive the following injection mixtures. Group-1: BEL in 1 side of the perioral area and BEL-L in the other side. Group-2: BEL in 1 side of the perioral area and BEL-LE in the other. Group-3: BEL-L in 1 side of the perioral and BEL-LE in the other (Figure 1A-C). In addition, in 15 patients the injection was started on the right side of the lips and in the other 15 patients it was started on the left side of the lips, in an alternating fashion. The trough of the cupid's bow was used as the dividing point between the 2 sides of the lips.

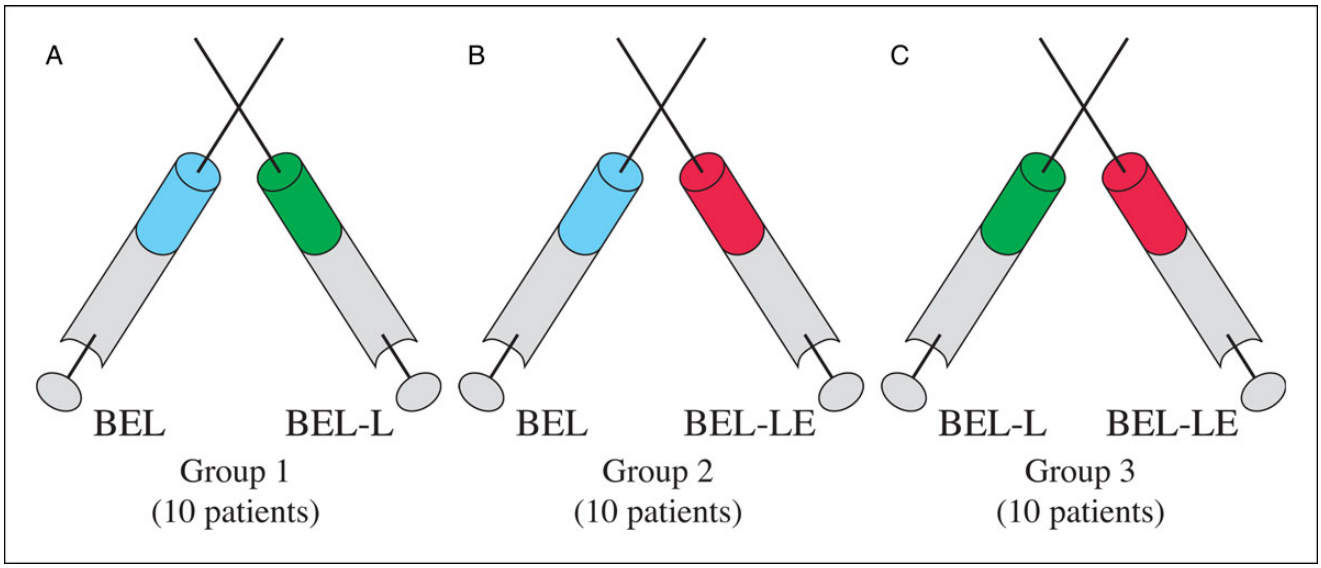

Figure 1. Allocations of soft tissue filler and anesthetic for cohesive polydensified matrix hyaluronic acid (CPMHA or BEL) and BEL with lidocaine (BEL-L) (A), BEL and BEL with lidocaine and epinephrine (BEL-LE) (B), and BEL-L and BEL-LE (C).

Immediately postinjection and postpain evaluation, the areas treated were gently massaged with the gloved thumb and index finger to assure there were no palpable bumps.

Evaluation

Adverse Events

The investigator evaluated all local and systemic adverse events at all visits, both through physical inspection of the patients and through anecdotal patient case histories.

Bruising

Assessment of bruising was performed on day 0 pretreatment, then at posttreatment day1, day 7 (±2 days) and day 14 (±2 days) by the blinded investigator (AM), using a 4-point nonvalidated scale, in which 0 represents "no visible bruising" and 3 represents "severe" bruising (Table 1). The blinded investigator, who is the lead author of the study, is a board-certified facial plastic surgeon with current and past involvement in several FDA studies evaluating dermal fillers. The patients (also blinded) used the bruising scale at the time of each follow-up visit to determine severity of bruising posttreatment. Using the same scale, at the end of the study the blinded evaluator (AS) reviewed and scored the patient photographs that were taken in random order on each visit (day 0, 1, 7, and 14). The blinded evaluator is a board-certified dermatologist with experience in injections and clinical research.

Table 1. Bruising Scale (0-3) Created by Treating Investigator and Used by Blinded Treating Investigator, Patients, and Blinded Evaluator

Score	Description	Characteristics
0	No change	No visible bruising
1	Mild	Visible on close inspection only confined within 5 mm of injection sites
2	Moderate	Easily visible within 5 mm to 10 mm of injection sites
3	Severe	Significant bruising, beyond 10 mm of injection sites

Pain

Patients were asked to score their pain levels immediately after completion of first-side treatment of the perioral lines. As soon as pain had been assessed, the contralateral side was treated, followed again by pain assessment immediately postinjection. Patients completed a nonvalidated Visual Analogue Scale, rating their pain in severity range from "no pain" to "agonizing pain." (See Figure 2).

Statistical Analysis

Descriptive statistics were used to quantify bruising and pain numerically. The study was not powered sufficiently to determine either the presence of absence of statistical significance (see Discussion).

RESULTS

Investigators assessed safety, bruising, and pain severity in this blinded, randomized, split-face study. Age range of the patients, all women, was 41 years to 72 years, with a mean of 52.6 years. No patients were lost to follow-up.

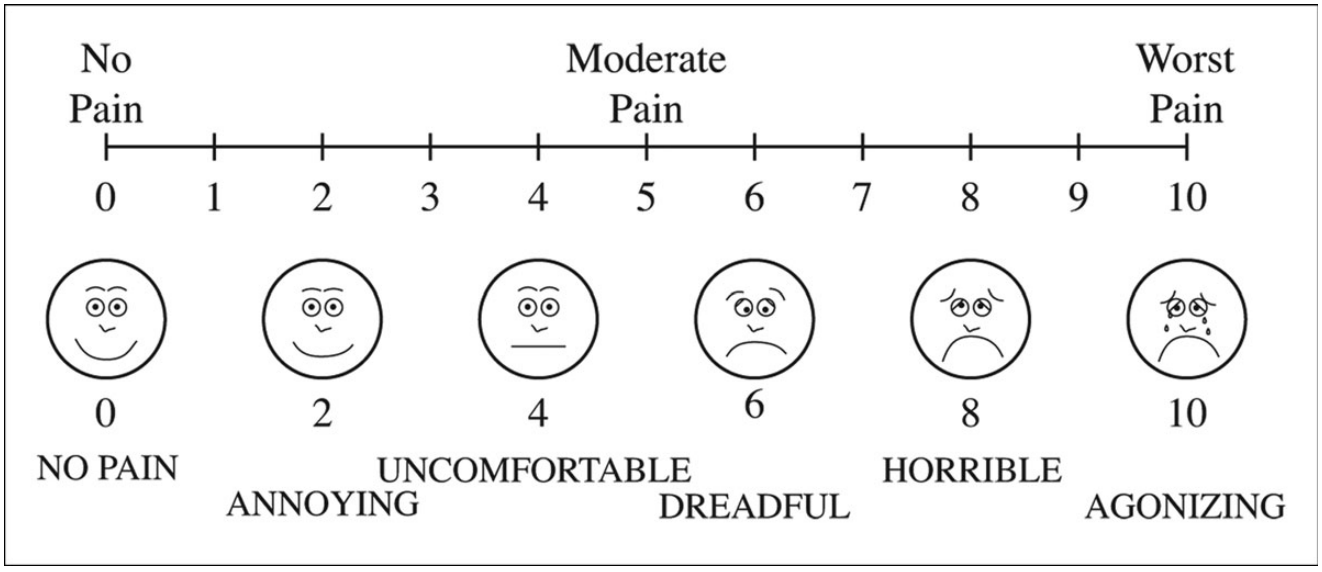

Figure 2. Visual analogue scale used by patients for determination of pain immediately post injection.

(The study was open to men but none expressed interest in participating).

Safety

No severe adverse events were reported by the patients or observed either by the investigator or the patient at any of the time points of the study. Bruising and pain were the most frequent events, reported by all patients. No lumps or nodules were reported either by the investigator or by the patient.

Bruising

Evaluation of bruising severity was made on day 0 at pretreatment and posttreatment, day 1, day 7, and day 14. Bruising was most pronounced on day 1, then declined by more than half by day 7, and had resolved in all patients by day 14.

Table 2. Bruising on Day 1 and Day 7 for BEL and BEL-L

Patient	Physician Investigator		Blinded Evaluator		Patients	
	BEL	BEL-L	BEL	BEL-L	BEL	BEL-L
Bruising scores for BEL vs BEL-L on day 1						
1-03	0	3	0	0	1	2
1-04	1	1	1	1	1	1
1-05	3	1	2	1	3	0
1-08	3	1	2	1	3	0
1-09	3	3	2	2	2	2
1-11	1	3	0	2	1	2
1-15	1	0	1	0	1	0
1-20	2	3	3	2	2	3
1-26	1	1	3	3	2	2
1-28	1	1	1	1	1	1
Mean	**1.6**	**1.7**	**1.5**	**1.3**	**1.7**	**1.3**
SD	**1.02**	**1.10**	**1.02**	**0.90**	**0.78**	**1.00**
Bruising scores for BEL vs BEL-L on day 7						
1-03	0	0	0	0	0	0
1-04	0	1	0	1	0	1
1-05	1	0	0	1	1	0
1-08	0	0	0	0	0	0
1-09	0	0	0	0	1	1
1-11	0	3	0	2	0	1
1-15	0	0	0	0	0	0
1-20	0	0	0	0	0	0
1-26	0	0	0	0	0	0
1-28	0	0	0	0	0	0
Mean	**0.1**	**0.4**	**0**	**0.4**	**0.2**	**0.3**
SD	**0.30**	**0.92**	**0.00**	**0.66**	**0.40**	**0.46**

BEL, cohesive polydensified matrix hyaluronic acid; BEL-L, cohesive polydensified matrix hyaluronic acid with lidocaine; SD, standard deviation.

Table 3. Bruising on Day 1 and Day 7 for BEL and BEL-LE

Patient	Physician Investigator		Blinded Evaluator		Patients	
	BEL	BEL-LE	BEL	BEL-LE	BEL	BEL-LE
Bruising scores for BEL vs BEL-LE on day 1						
1-02	2	2	2	2	2	3
1-06	1	0	1	0	1	0
1-07	1	0	1	1	1	1
1-10	3	1	2	1	3	1
1-13	1	1	2	1	1	1
1-14	1	3	1	2	2	2
1-17	0	1	0	1	0	2
1-24	1	1	0	2	1	1
1-25	1	0	1	1	1	1
1-27	3	2	2	1	2	2
Mean	**1.4**	**1.1**	**1.2**	**1.2**	**1.4**	**1.4**
SD	**0.92**	**0.94**	**0.75**	**0.60**	**0.80**	**0.80**
Bruising scores for BEL vs BEL-LE on day 7						
1-02	2	2	2	2	1	1
1-06	1	0	1	0	1	0
1-07	0	0	0	0	0	0
1-10	3	0	1	0	2	1
1-13	0	0	0	0	0	0
1-14	1	0	0	0	0	1
1-17	0	0	0	0	0	0
1-24	1	1	1	1	1	1
1-25	1	0	1	0	1	1
1-27	0	0	1	0	0	0
Mean	**0.9**	**0.3**	**0.7**	**0.3**	**0.6**	**0.5**
SD	**0.94**	**0.64**	**0.64**	**0.64**	**0.66**	**0.50**

BEL, cohesive polydensified matrix hyaluronic acid; BEL-LE, cohesive polydensified matrix hyaluronic acid with lidocaine and epinephrine; SD, standard deviation.

Bruising reported for each mixture is shown in Tables 2-4. Bruising scores for day 0 and day 14 were 0 for each patient and consequently are not shown; bruising scores for days 1 and 7 are shown for each of the preparations. Regardless of the mixture, the evaluations by the blinded treating physician investigator (PI), blinded patients, and blinded evaluator were similar across cohorts. Figure 3 shows the aggregate scores by cohort.

Figure 4 shows representative bruising on day 0, day 1, day 7, and day 14. Figures 5-7 show day 1 and day 7 series of images of 3 patients treated with either BEL-LE and BEL, or BEL-L and BEL, or BEL-L and BEL-LE.

Pain

Evaluation of pain was recorded by patients immediately postinjection in 1 side of the face and then immediately

Table 4. Bruising on Day 1 and Day 7 for BEL-L and BEL-LE

Patient	Physician Investigator		Blinded Evaluator		Patients	
	BEL-L	BEL-LE	BEL-L	BEL-LE	BEL-L	BEL-LE
Bruising scores for BEL-L vs BEL-LE on day 1						
1-01	2	1	1	0	2	1
1-12	1	0	0	0	1	0
1-16	2	3	2	3	2	3
1-18	1	1	1	1	1	1
1-19	3	3	3	3	2	2
1-21	0	1	1	1	0	1
1-22	2	1	3	2	2	1
1-23	1	0	1	1	0	0
1-29	2	2	2	3	2	2
1-30	2	2	2	2	1	2
Mean	**1.6**	**1.4**	**1.6**	**1.6**	**1.3**	**1.3**
SD	**0.80**	**1.02**	**0.92**	**1.11**	**0.78**	**0.90**
Bruising scores for BEL-L vs BEL-LE on day 7						
1-01	0	0	0	0	0	0
1-12	0	0	0	0	0	0
1-16	1	3	0	2	1	2
1-18	0	0	1	1	0	1
1-19	0	0	1	1	0	0
1-21	0	0	0	0	0	0
1-22	0	0	1	0	0	0
1-23	0	0	0	0	0	0
1-29	0	0	0	0	1	1
1-30	0	0	1	1	1	1
Mean	**0.1**	**0.3**	**0.4**	**0.5**	**0.3**	**0.5**
SD	**0.30**	**0.90**	**0.49**	**0.67**	**0.46**	**0.67**

BEL-L, cohesive polydensified matrix hyaluronic acid with lidocaine; BEL-LE, cohesive polydensified matrix hyaluronic acid with lidocaine and epinephrine; SD, standard deviation.

post injection in the other side of the face. Table 5 shows the patients' pain scores for each of the 3 cohorts. Figure 8 illustrates the aggregate pain scores for each of the 3 preparations.

DISCUSSION

We sought to strengthen the validity of the comparisons reported here through use of a split-face, randomized, blinded study design. The different preparations to be injected were delivered in identical syringes, so that only the assistant knew which syringe contained which preparation. Given our awareness about the small size of the treatment cohorts, we deliberately injected 1 mL of blinded preparations into each side to control as much as possible for preparation and/or injector bias toward 1 of the 3 preparations and against the other 2. In regard to the preparations, investigators attempted to simulate the volume

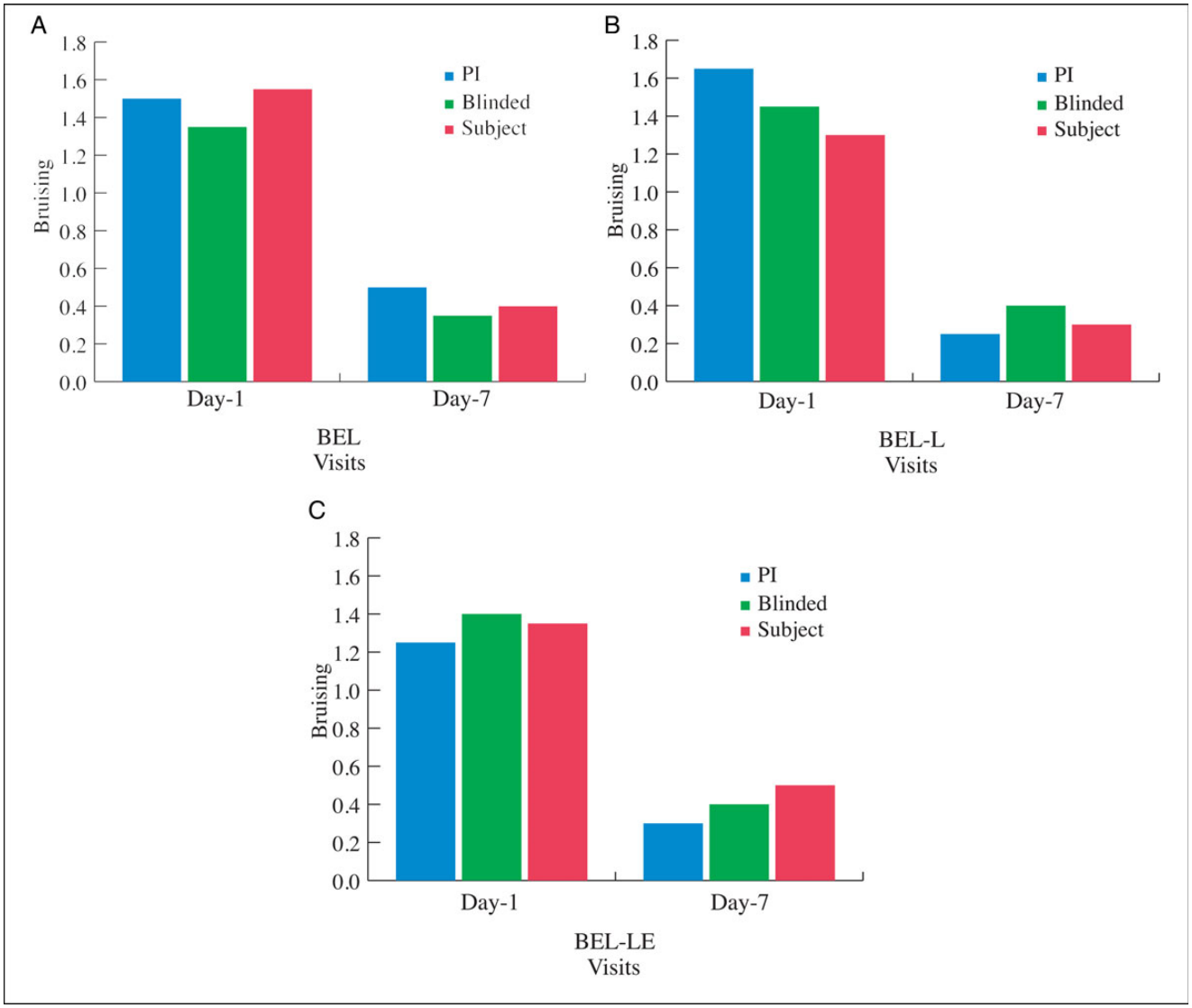

Figure 3. Aggregate bruising scores by physician investigator (PI), blinded evaluator, and patients for all 3 preparations.

dilution effect of the lidocaine (and epinephrine) through volumes of each that the investigators use in clinical practice. The addition of a very small amount of sterile water to the BEL syringe to control for minor volume differences was considered but discounted since the investigators wanted to mimic the clinical use of the HA as much as possible.

Lack of validation of a posttreatment-bruising scale warrants comment. Although the bruising scale used in this study has not been validated, it should be noted that the ratings by the patients do not differ widely from the ratings by the 2 evaluators. We believe that the similarities in rating scores by the blinded evaluator, the blinded treating investigator, and the patients support the reliability of the scales as a measure of bruising. Figure 3 also shows the narrow range of bruising scores across cohorts. We are heartened by the rating similarities across all evaluator segments but are hard-pressed to elaborate on inter-rater consistency, given the sample size.

Not unlike the results found with evaluation of bruising, the differences in perceived pain were similar across all 3 cohorts in the study. This supports the fact that the effect of lidocaine is not instantaneous; some time is required for the lidocaine to enter the neuronal membrane where it asserts its effect. In addition, although we planned for control of bruising, we could not plan for bias of pain on the part of the patients. One effort to control for pain bias was to avoid the use of topical anesthetic products, with their inherent confounding variations (eg, different types of anesthetics, amount used per square inch, duration of application, and varying absorption rates). Without topical anesthesic and without awareness of which preparation

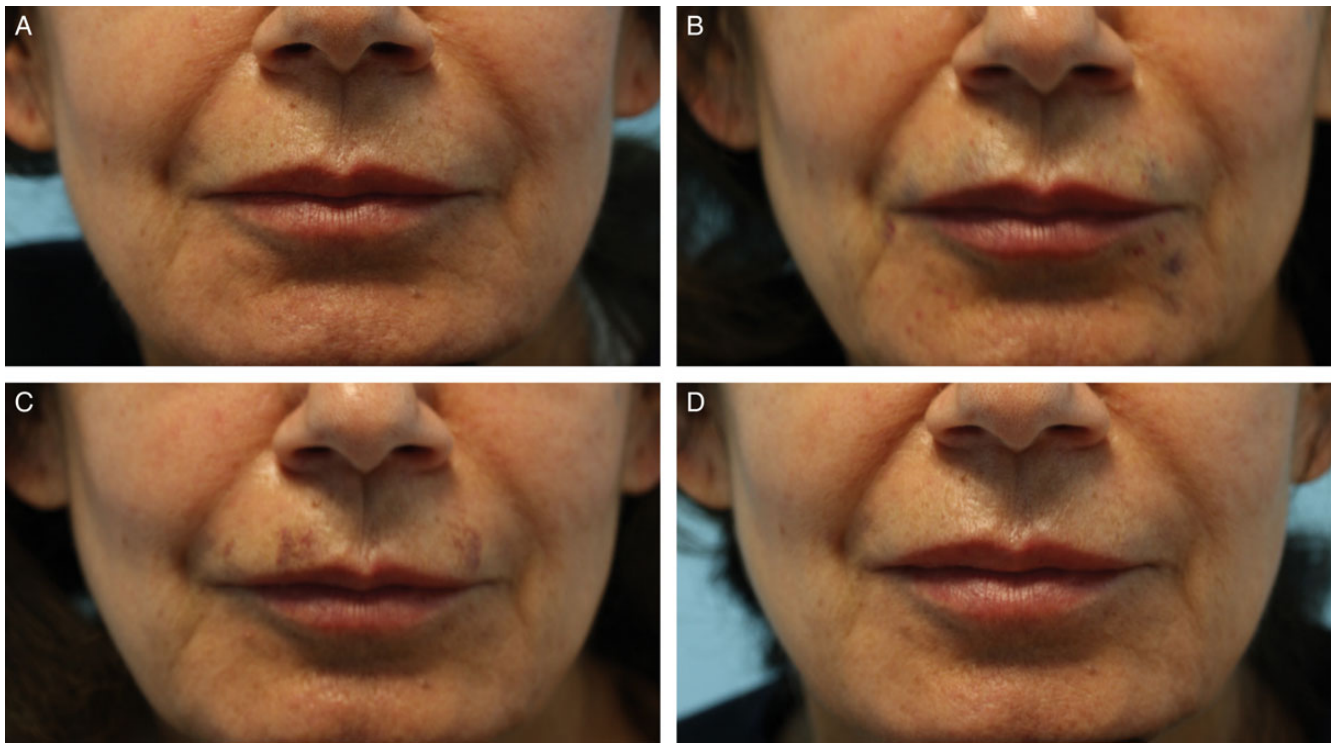

Figure 4. Representative bruising on day 0 (A), day 1 (B), day 7 (C), and day 14 (D) in this 72-year-old woman. Patient received BEL (cohesive polydensified matrix hyaluronic acid or CPMHA) in right (R) and BEL-LE (CPMHA with lidocaine and epinephrine) in left (L). Scores on day 0 and day 14 were 0. Scores on day 1 were R-2, L-3 (physician investigator), R-2, L-2 (blinded evaluator), and R-2, L-2 (patient). On day 7, scores were R-2, L-2 (physician investigator), R-2, L-2 (blinded evaluator), and R-1, L-1 (patient).

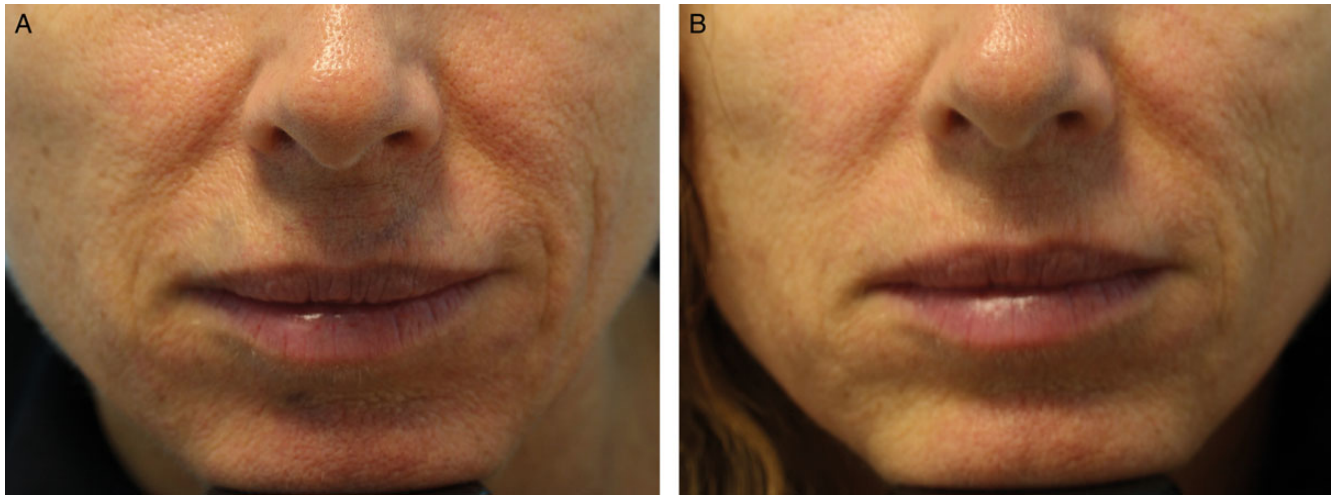

Figure 5. This 50-year-old woman received 1.0 mL of BEL-LE (cohesive polydensified matrix hyaluronic acid with lidocaine and epinephrine) in her right perioral area and 1.0 mL of BEL in her left perioral area. Day 1 (A) and Day 7 (B) images were obtained. All scores by physician investigator (PI), blinded evaluator, and patients were 0 on day 0 and day 14. PI scores on day 1 were 1 (R, right) and 1 (L, left) and 0 (R) and 0 (L) on day 7. Blinded evaluator scores on day 1 were 1 (R) and 2 (L) and 0 (R) and 0 (L) on day 7. Patient scores on day 1 were 1 (R) and 1 (L) and 0 (R) and 0 (L) on day 7.

was in which syringe, the patients rated pain in each side. The patients knew they were part of a study; whether that knowledge influenced them to lower (or increase) their assessment of pain cannot be determined. In addition, cannulas were not used because of concerns about depth of injection of the dermal fillers in the superficial perioral lines.

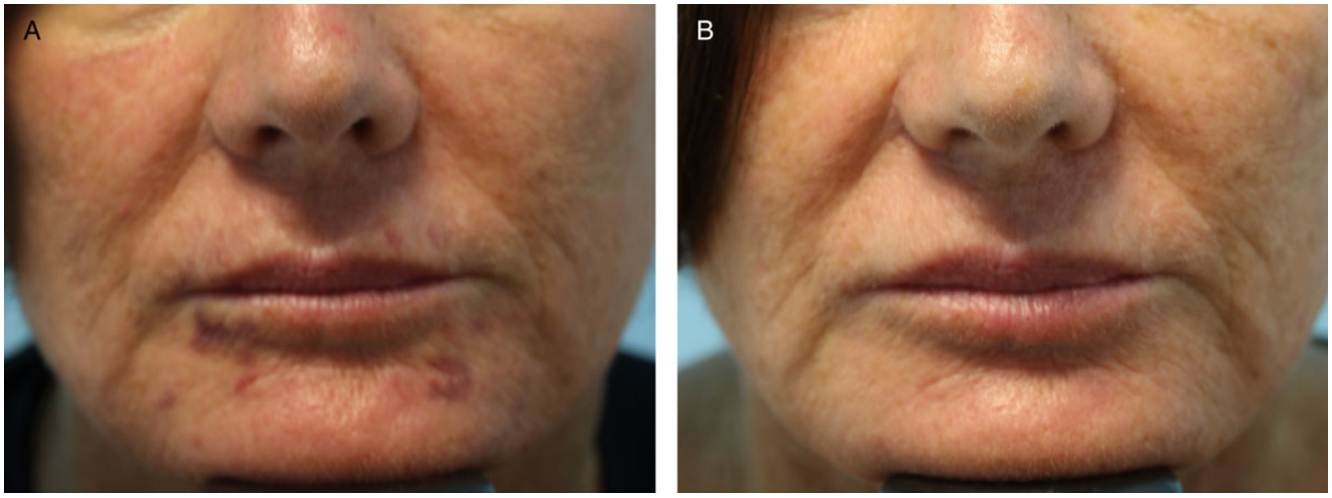

Figure 6. This 61-year-old woman received 1.0 mL of BEL-L (cohesive polydensified matrix hyaluronic acid with lidocaine) in her right perioral area and 1.0 mL of BEL in her left perioral area. Day 1 (A) and day 7 (B) images were obtained. All scores by physician investigator (PI), blinded evaluator, and patients were 0 on day 0 and day 14. PI scores on day 1 were 3 (R, right) and 2 (L, left) and 0 (R) and 0 (L) on day 7. Blinded evaluator scores on day 1 were 2 (R) and 3 (L) and 0 (R) and 0 (L) on day 7. Patient scores on day 1 were 3 (R) and 2 (L) and 0 (R) and 0 (L) on day 7.

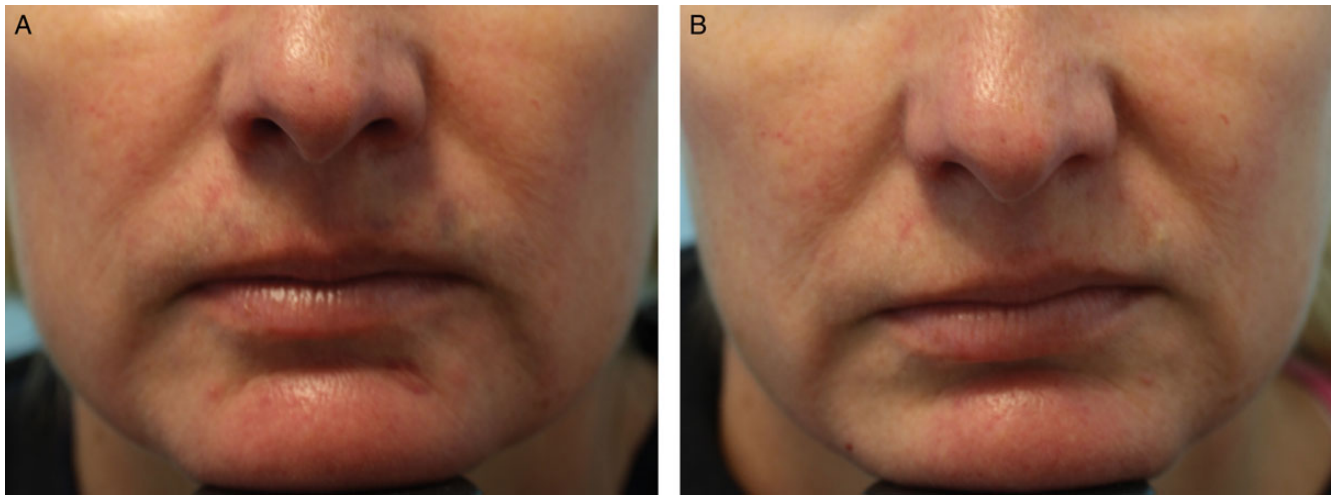

Figure 7. This 41-year-old woman received 1.0 mL of BEL-L (cohesive polydensified matrix hyaluronic acid with lidocaine) in her right perioral area and 1.0 mL of BEL-LE (BEL-L with epinephrine) in her left perioral area. Day 1 (A) and day 7 (B) images were obtained. All scores by physician investigator (PI), blinded evaluator, and patient were 0 on day 0 and day 14. PI scores on day 1 were 2 (R, right) and 2 (L, left) and 0 (R) and 0 (L) on day 7. Blinded evaluators scores on day 1 were 2 (R) and 2 (L) and 1 (R) and 1 (L) on day 7. Patient scores on day 1 were 1 (R) and 2 (L) and 1 (R) and 1 (L) on day 7.

Consequently, the role of pain reduction through the use of cannulas was not explored.

The finding of little difference in pain between BEL and BEL-L is unusual and, to no small extent, contradictory to other publications and experiences of hyaluronic acids injected with lidocaine.[18,27-34] We have always used lidocaine in our clinical practice for ease of injection and reduction of pain. The limited benefit of lidocaine in this investigator-initiated small study could be partly due to the treating investigator not waiting long enough for the lidocaine to fully take effect as well as to the increased pain in 1 area of the face (eg, the perioral lines) compared to another area (eg, the NLFs). In addition, we confined our evaluation of pain to the superficial dermis. Whether pain results in the deep dermis would be different cannot be determined from this study. Our study was designed to measure perioral pain only immediately posttreatment and bruising over a period of 2 weeks. To that end, we assessed pain 1 time

Table 5. Evaluation of Pain by Patients Immediately Posttreatment in Each Side of the Face

Patient	BEL-L	BEL-LE	Patient	BEL	BEL-LE	Patient	BEL	BEL-L
Pain scores								
1-01	5	4	1-02	4	3	1-03	4	2
1-12	2	0	1-06	4	2	1-04	3	2
1-16	5	5	1-07	4	5	1-05	8	5
1-18	3	2	1-10	6	5	1-08	4	5
1-19	3	4	1-13	6	5	1-09	2	3
1-21	5	7	1-14	8	8	1-11	2	2
1-22	3	4	1-17	2	5	1-15	4	5
1-23	2	2	1-24	8	6	1-20	3	2
1-29	5	4	1-25	3	3	1-26	10	7
1-30	3	4	1-27	8	4	1-28	5	5
Mean	**3.6**	**3.6**	**Mean**	**5.3**	**4.6**	**Mean**	**4.5**	**3.8**
SD	**1.26**	**1.90**	**SD**	**2.21**	**1.71**	**SD**	**2.59**	**1.81**

BEL, cohesive polydensified matrix hyaluronic acid; BEL-L, cohesive polydensified matrix hyaluronic acid with lidocaine; BEL-LE, cohesive polydensified matrix hyaluronic acid with lidocaine and epinephrine; SD, standard deviation.

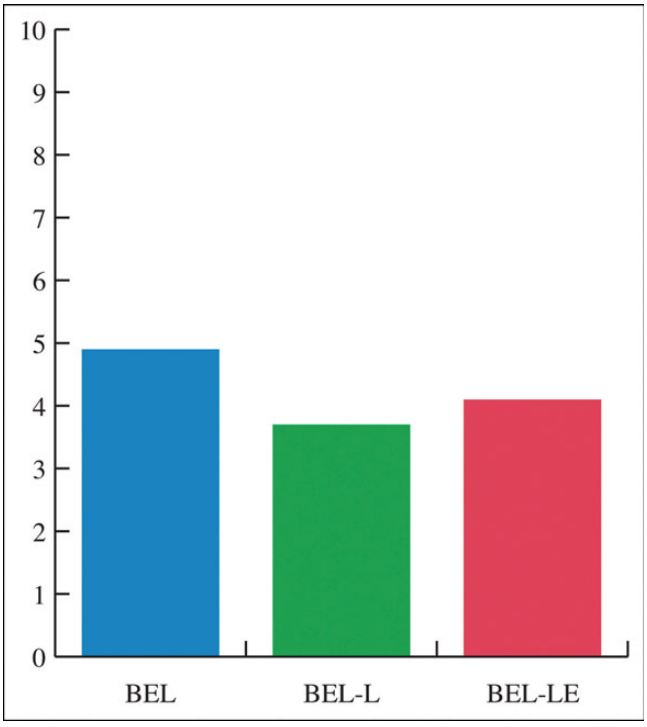

Figure 8. Aggregate patient pain scores for each preparation, with 0 representing no pain, 5 representing moderate pain, and 10 representing worst pain.

and bruising 4 times. In a study published several years ago, investigators asked 45 NLF-injected patients to rate their pain levels at 5 time intervals over an hour.[31] Whether the pain scores in our study would have more closely mirrored beneficial findings of lidocaine use in the earlier study is not known.

At the present time, many injectors continue to mix the dermal fillers they use with lidocaine and at times with epinephrine as well to decrease bruising. We acknowledge the inherent limitations associated with small sample populations and have tried to anticipate these in our attention to randomization and blinding. Powering the study for the possibility of statistical difference remains a concern. Our study lacked the power to determine statistical differences across the cohorts. This is an investigator-initiated study of 30 patients at 1 study site; developing a patient population sufficient for statistical significance is beyond the scope of a study that, from the outset, was intended to be a source for hypothesis generating rather than providing any definitive conclusions.

We believe this study could be helpful in shaping the protocols for larger studies of pain and bruising postinjection of dermal fillers that would either invalidate or support the tentative findings reported here. In this study, the effect of the differences in preparations is difficult to quantify due to sample size; larger population studies may be required to

demonstrate statistical, as well as clinically meaningful, differences.

CONCLUSIONS

Based on our study in the correction of lip lines, we observed no significant differences in pain or bruising when lidocaine or lidocaine and epinephrine were added to BEL. Future studies may explore many different variables such as different facial regions and different concentrations of lidocaine.

Disclosures

Dr Moradi is a paid speaker, consultant, and advisory board member for Allergan, Inc (Irvine, California), Galderma Laboratories (Ft Worth, Texas), SkinMedica (Carlsbad, California, and Merz North America (Raleigh, North Carolina). The other authors declared no conflicts of interest with respect to the research, authorship, and publication of this article.

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REFERENCES

1. Cohen JL, Dayan SH, Brandt FS, et al. Systematic review of clinical trials of small- and large-gel-particle hyaluronic acid injectable fillers for aesthetic soft tissue augmentation. *Dermatol Surg*. 2013;39(2):205-31.
2. Coleman SR. Facial augmentation with structural fat grafting. *Clin Plast Surg*. 2006;33(4):567-577.
3. Moradi A, Shirazi A, Moradi J. A 12-month, prospective, evaluator-blinded study of small gel particle hyaluronic acid filler in the correction of temporal fossa volume loss. *Jnl of Drugs Dermatol*. 2013;12(4):470-475.
4. Gilchrest BA. Photoaging. Review. *J Invest Dermatol*. 2013;133(E1):E2-E6. .
5. Wilhelmi BJ, Blackwell SJ, Phillips LG. Langer's lines: to use or not to use. *Plast Reconstr Surg*. 1999;104(1):208-214.
6. Package Insert. Belotero Balance®. Greensboro, NC: Merz North America, 2012.
7. Downie JB, Grimes PE, Callender VD. A multicenter study of safety and efficacy of the hyaluronic acid with a cohesive polydensified matrix for treatment of nasolabial folds in subjects with Fitzpatrick Skin Types IV, V, and VI. *Plast Recon Surg*. 2013;132:41S-47S.
8. Narins RS, Coleman W III, Donofrio L, et al. Nonanimal sourced hyaluronic acid-based dermal filler using a cohesive polydensified matrix technology is superior to bovine collagen in the correction of moderate to severe nasolabial folds: results from a 6-month, randomized, blinded, controlled, multicenter study. *Dermatol Surg*. 2010;36:730-740.
9. Narins RS, Coleman W III, Donofrio L, et al. Improvement in nasolabial folds with a hyaluronic acid filler using a cohesive polydensified matrix technology: results from an 18-month open-label extension trial. *Dermatol Surg*. 2010;36:1800-1808.
10. Prager W, Wissmüller E, Havermann I, et al. A prospective, split-face, randomized, comparative study of safety and 12-month longevity of three formulations of hyaluronic acid dermal filler for treatment of nasolabial folds. *Dermatol Surg*. 2012;38:1143-1150.
11. Kühne U, Imhof M, Kirchmeir M, Howell DJ. Five-year retrospective review of safety, injected volumes, and longevity of the hyaluronic acid Belotero Basic for facial treatments in 317 patients. *J Drugs Dermatol*. 2012;11:1032-1035.
12. Lorenc ZP, Fagien S, Fkynn TC, Waldorf HA. Clinical application and assessment of Belotero: A roundtable discussion. *Plast Recon Surg*. 2013;132:69S-676.
13. Busso M, Applebaum D. Hand augmentation with Radiesse (calcium hydroxylapatite). *J Dermatol Ther*. 2007;20:315-317.
14. Injectable implant instructions for use. RADIESSE® Web site. http://www.radiesse.com/wp-content/uploads/RADIESSE_Wrinkle_Filler_Instructions_for_Use.pdf. Accessed February 4, 2015.
15. Premarket Approval (PMA). US Food and Drug Administration Web site. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id = 14059. Accessed February 4, 2015.
16. Brandt F, Bank D, Cross SL, Weiss R. A lidocaine-containing formulation of large-gel particle hyaluronic acid alleviates pain. *Dermatol Surg*. 2010;36(s3):1876-1885.
17. Weiss R, Bank D, Brandt F. A randomized, double-blind, split-face study of small-gel particle hyaluronic acid with and without lidocaine during correction of nasolabial fold. *Dermatol Surg*. 2010;36(s1):750-756.
18. Weinkle SH, Bank DE, Boyd CM, Gold MH, Thomas JA, Murphy DK. A multi-center, double-blind, randomized controlled study of the safety and effectiveness of Juvéderm®injectable gel with and without lidocaine. *J Cosmet Dermatol*. 2009;8:205-210.
19. Sheets MF, Hanck DA. Outward stabilization of the S4 segments in domains III and IV enhances lidocaine block of sodium channels. *J Physiol*. 2007;582(Pt 1):317-334. Epub 2007 May 17.
20. McNulty MM, Edgerton GB, Shah RD, Hanck DA, Fozzard HA, Lipkind GM. Charge at the lidocaine binding site residue Phe-1759 affects permeation in human cardiac voltage-gated sodium channels. *J Physiol*. 2007;581(Pt 2):741-755. Epub 2007 Mar 15.
21. Scheuer T. Local anaesthetic block of sodium channels: raising the barrier. *J Physiol*. 2007;581(Pt 2):423. Epub 2007 Apr 5.
22. Sheets MF, Fozzard HA, Lipkind GM, Hanck DA. Sodium channel molecular conformations and antiarrhythmic drug affinity. *Trends Cardiovasc Med*. 2010;20(1):16-21.

23. Dochery RJ, Farmer CE. The pharmacology of voltage-gated sodium channels in sensory neurons. *Handb Exp Pharmacol*. 2009;194:519-561.
24. Fabi SG, Champagne JP, Nettar KD, Maas CS, Goldman MP. Efficacy and safety of and patient satisfaction with injectable hyaluronic acid with 0.3% lidocaine hydrochloride for the treatment of superficial perioral lines or superficial lateral canthal lines. *Dermatol Surg*. 2013;39 (11):1613-1620.
25. Beasley KL, Weiss MA, Weiss RA. Soft tissue augmentation using a two-way connector to supplement hyaluronic acid filler with 1% lidocaine acid with epinephrine 1:100,000: Our experience and observations. *Dermatol Surg*. 2010;36(4):524-526.
26. Matarasso SL, Carruthers JD, Jewell ML, et al. Consensus recommendations for soft-tissue augmentation with non-animal stabilized hyaluronic acid (Restylane). *Plast Recon Surg*. 2006;117(Suppl):3S-34S.
27. Sarnoff D, Saini R, Gotkin R. Comparison of filling agents for lip augmentation. *Aesthet Surg J*. 2008;28(5):556-562.
28. Redbord KP, Busso M, Hanke CW. Soft-tissue augmentation with hyaluronic acid and calcium hydroxylapatite fillers. *Dermatol Ther*. 2011;24:71-81.
29. Allemann IB, Baumann L. Hyaluronic acid gel (Juvederm™) preparations in the treatment of facial wrinkles and folds. *Clin Inter Aging*. 2008;3(4):629-634.
30. Smith K. Practical uses of Juvederm: Early experience. *Plast Recon Surg*. 2007;120(6S):67S-73S.
31. Fagien S, Maas C, Murphy DK, Thomas JA, Beddingfield FC. Juvederm for lip enhancement An open-label, multinational study. *Aesthet Surg J*. 2013;33(3):414-420.
32. Levy PM, de Boulle K, Raspaldo H. Comparison of injection comfort of a new category of cohesive hyaluronic acid filler with preincorporated lidocaine and a hyaluronic acid filler alone. *Dermatol Surg*. 2009;35 (Suppl 1):332-336. discussion 337.
33. Monheit GD, Campbell RM, Neugent H, et al. Reduced pain with use of proprietary hyaluronic acid with lidocaine for correction of nasolabial folds: a patient-blinded, prospective, randomized controlled trial. *Dermatol Surg*. 2010;36(1):94-101.
34. Lupo MP, Swetman G, Waller W. The effect of lidocaine when mixed with large gel particle hyaluronic acid filler tolerability and longevity: a six-month trial. *J Drugs Dermatol*. 2010;9(9):1097-1100.
35. Wahl G. European evaluation of a new hyaluronic acid filler incorporating lidocaine. *J Cosmet Dermatol*. 2008;7 (4):298-303.
36. Smith L, Cockerham K. Hyaluronic acid dermal fillers: can adjunctive lidocaine improve patient satisfaction without decreasing efficacy or duration? *Patient Prefer Adherence*. 2011;5:133-139.