

An Investigation of Changes in Physical Properties of Injectable Calcium Hydroxylapatite in a Carrier Gel When Mixed with Lidocaine and with Lidocaine/Epinephrine

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INTRODUCTION As physicians incorporate calcium hydroxylapatite (CaHA) into their aesthetic treatment regimens, the question has arisen of whether the addition of anesthetic agents to prefilled CaHA syringes might provide sufficient anesthetic prophylaxis to warrant reduction in conventional anesthetic pretreatment procedures.

STUDY DESIGN Investigators sought to determine changes in the physical properties of CaHA induced by the addition of lidocaine and lidocaine with epinephrine into the prefilled CaHA syringe. The CaHA and gel carrier (CHM) were mixed with varying amounts of lidocaine and lidocaine with epinephrine to measure the number of passes back and forth for optimal homogeneity of lidocaine and CaHA in syringes, changes in viscosity, extrusion force, needle jam rates, elasticity, and pH.

RESULTS Ten mixing passes appeared sufficient for homogeneity. Viscosities and extrusion forces of CHM/lidocaine blends decrease with increasing amount of lidocaine. Needle jams do not increase. The pH and elasticity of the CHM/lidocaine blend are essentially equivalent to those of CHM alone. Epinephrine added to lidocaine did not alter the results enough to reach statistical significance.

CONCLUSIONS Addition of lidocaine to original CHM can be safely added without harmful changes in physical properties of the original soft tissue filler. Further studies are required to explore whether the addition of lidocaine to CHM alters patient discomfort, durability, and efficacy.

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Radiesse (BioForm Medical Inc., San Mateo, CA) is a soft tissue filler consisting of calcium hydroxylapatite (CaHA) microspheres, 25 to 45 μ m in diameter, and a sodium carboxymethyl cellulose (CMC) carrier gel. Collectively, these two elements constitute the CaHA media, referred to herein as CHM. The filler is usually injected through a 25- to 27-gauge needle, 0.5 to 1.5 inches in length. Over a period of several weeks, the CMC is replaced by fibroblasts and extracellular matrix, leaving the CaHA microspheres in place to provide mechanical support.¹ Even though individual CaHA microspheres are radioopaque, moderate injection amounts do not disrupt most radiographic analysis.²

CHM is currently approved for treatment of severe facial folds and wrinkles, such as nasolabial folds,

and for treatment of human immunodeficiency virus-associated facial lipoatrophy. Durability is estimated ranging from 10 to 18 months.³⁻⁶

Additional uses of the product in the correction of marionette lines, oral commissures, prejowl sulcus, acne scarring, cheeks augmentations, infraorbital rim, and temporal hollows have been reported.^{5,7-13}

Late in 2007, Busso and Applebaum¹⁴ published a report of their experiences in combining CHM with lidocaine for off-label use of the soft tissue filler in treatment of the hand. In the report, Busso and Applebaum briefly explained how mixing the two compounds together appeared to considerably lessen discomfort in patients receiving a bolus of the mixture for hand rejuvenation and augmentation. Busso and Applebaum observed that 0.15 mL of 2% lido-

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caine per 1.3-mL syringe of CHM was the minimum amount of anesthetic that appeared to yield adequate anesthesia without excessive loss of physical properties. A number of other physicians are adopting the technique of Busso and Applebaum technique for mixing CHM with standard 2% lidocaine-HCl solutions, mixing between 0.05 and 0.40 mL of lidocaine with a 1.3-mL syringe of CHM.¹⁵ Mixing 0.23 mL of 2% lidocaine solution with 1.3 mL of CHM yields 0.3% lidocaine concentration. This concentration is equivalent to that found in other soft tissue fillers, such as Zyderm and CosmoPlast.^{16,17}

Not only do the individual volumes of lidocaine differ in this off-label application of CHM by physicians, but the mixing techniques are physician-specific as well. Some physicians draw the lidocaine directly into the syringe of CHM; others mix lidocaine and CHM with a nose-to-nose Luer-lok connector. Some physicians barely mix the lidocaine with CHM, while others mix to produce a homogeneous media. The effects of these mixing techniques on the performance of CHM are unclear.

To characterize the effects of various lidocaine volumes and mixing techniques on CHM, the physical properties of CHM blended with 2% lidocaine-HCl solutions were measured. The results detailed below should help physicians better understand the properties of CHM mixed with lidocaine solutions.

Study Purpose and Design

This study sought to characterize the physical properties of CHM combined with plain 2% lidocaine-HCl solutions and combined with 2% lidocaine-HCl solutions and 10 µg epinephrine—under various mixing conditions. Researchers studied a range of lidocaine concentrations, described below, to compare the dynamic viscosity, extrusion force, and needle jamming rate of the mixtures compared to those of commercially available CHM. Investigators also evaluated the dynamic viscosity of the mixtures at the front, middle, and back of each mixed syringe of lidocaine and CHM, as a measure of mixing

efficiency. In addition, they compared the results of CHM mixed with lidocaine to those of CHM mixed with lidocaine and epinephrine.

Materials/Equipment

CHM (Radiesse, BioForm Medical Inc) was commercially available material. The nominal fill volume per syringe was 1.3 mL as shown by product labeling. Testing was completed using from 3 to 12 different commercially available lots of CHM for each test condition.

The 2% lidocaine solution was composed of anhydrous lidocaine-HCl (20 mg/mL), NaCl (6 mg/mL), and methylparaben (1 mg/mL; Hospira, Lake Forest, IL). The 2% lidocaine solution with epinephrine was composed of anhydrous lidocaine-HCl (20 mg/mL), epinephrine (10 µg/mL), NaCl (6 mg/mL), sodium metabisulfite (0.5 mg/mL), citric acid (0.2 mg/mL), and methylparaben (1 mg/mL; Hospira).

A rheometer (Haake RS-600, Thermo-Fisher, Newton, NH) measured dynamic viscosity of the media. Extrusion force was measured by a materials tester (R5K Plus, Lloyd Instruments, Fareham, Hampshire, UK). Media pH was measured using a pH meter with a probe (Model 720A and SureFlow probe, respectively, Orion Instruments, Baton Rouge, LA). The female-to-female Luer-lok connectors used to connect the mixing and media syringes were Ark-Plas Part No. AP18FLXFEP (Flippin, AR).

Procedures

During the course of the study and at each test condition, researchers examined a 1.3-mL syringe of CHM, mixed with one of four volumes of 2% lidocaine or 2% lidocaine plus epinephrine solution:

- 0.05 mL (0.07% final lidocaine-HCl);
- 0.10 mL (0.14% final lidocaine-HCl);
- 0.15 mL (0.21% final lidocaine-HCl);
- 0.23 mL (0.30% final lidocaine-HCl).

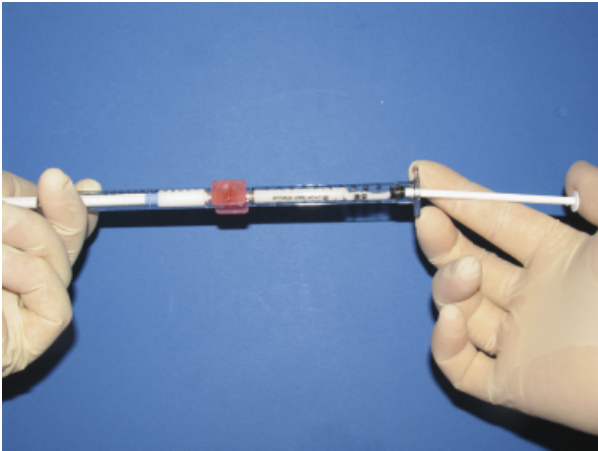


Figure 1. CHM mixed with lidocaine, using a female-to-female Luer-lok connector. (Photo courtesy of Mariano Busso, MD; used by permission of Blackwell Publishing Inc.)

Because the graduations on the tuberculin syringe are more accurate than those on a standard 1.3-mL syringe, the lidocaine solution was withdrawn from a 50-mL vial with a 1.0-mL tuberculin syringe (Becton Dickinson [B-D], Franklin Lakes, NJ) fitted with a 0.5-inch, 27-gauge B-D needle. The lidocaine solution was then injected from the tuberculin syringe into the nose of a BioForm 1.3 mL syringe (mixing syringe). The push rod of the mixing syringe was depressed to remove all excess air and then the mixing syringe with lidocaine was firmly connected to a syringe of CHM using a female-to-female Luer-lok connector (Figure 1).

Lidocaine and CHM were mixed by alternately depressing the plungers on the mixing and media syringes for 2, 5, or 10 mixing strokes. Each mixing stroke was composed of one complete compression of the CHM syringe push rod, followed by one complete compression of the mixing syringe push rod. Push rods were compressed firmly and quickly, at approximately two compressions per second. Following mixing, the mixing syringe and Luer-lok connector were removed and discarded, and the lidocaine/CHM mixture was recapped with the original media syringe cap. The CHM and lidocaine blends were tested between 15 minutes and 2 hours after mixing with lidocaine.

Nine rheology replicates, 12 extrusion force replicates, and at least three pH replicates were conducted per test condition. Rheology was evaluated with a 20-mm titanium rotor, with a gap of 2.0 mm and τ of 5 N, over a frequency sweep of 0.1 to 10 Hz evaluated at 0.6 and 5.0 Hz. Extrusion force was evaluated through 27-gauge, 0.5-inch B-D needles, with an extension rate of 2 inches per minute. Media pH was obtained by completely coating the glass bulb of the pH probe with media, spreading or smoothing the media with a plastic spatula as necessary.

To evaluate the extent of mixing under different conditions, rheology and pH were tested for media from the front (hub), middle, or back (plunger) of the syringe barrel. Approximately 0.4 mL of media from the front, middle, or back of two syringes was combined for each measurement.

Results

Investigators evaluated seven test conditions in the study: 1) number of passes between syringes sufficient for blending lidocaine and CHM; 2) changes in viscosity with differing concentrations of lidocaine; 3) extrusion forces of lidocaine and CHM, compared to CHM alone; 4) incidence of needle jamming in lidocaine/CHM blend; 5) pH of lidocaine/CHM compared to CHM alone; 6) viscosity and elasticity of CHM and lidocaine compared to CHM and lidocaine with epinephrine; and 7) extrusion force of CHM and lidocaine compared to CHM and lidocaine with epinephrine.

1. Number of Passes between Syringes Sufficient for Blending Lidocaine and CHM

Figure 2 shows the percentage difference from the mean for the dynamic viscosity at 0.6 Hz under various mixing conditions. With “adequate mixing” defined as a percentage difference less than 10% for media across all regions of the syringe, 10 mixing passes provided adequate mixing for all lidocaine volumes tested. Five mixing passes provided adequate

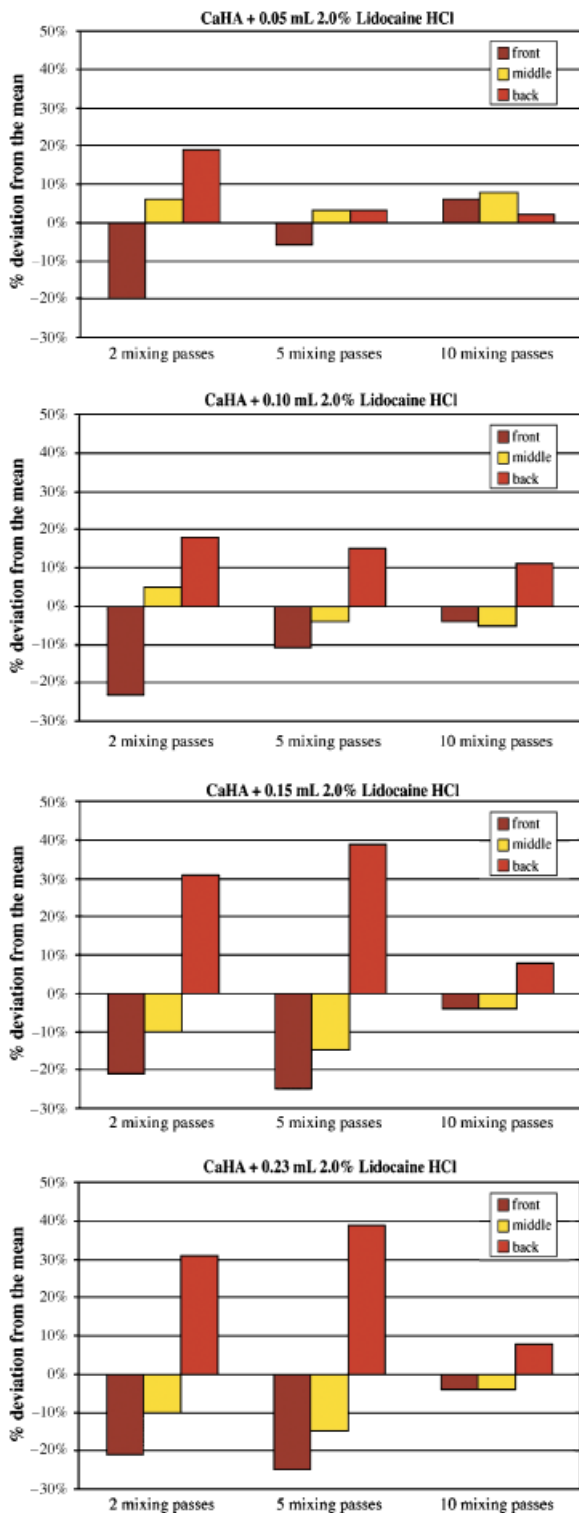


Figure 2. Percentage differences in distribution of four separate volumes of lidocaine with CHM, under three mixing conditions.

mixing for 0.05 mL of lidocaine solution, but not for the other volumes. Two mixing passes did not provide adequate mixing for any volume tested, with the net front-to-back spread ranging from 39% at 0.05 mL of lidocaine, up to 52% at 0.23 mL of lidocaine.

The magnitude of the front-to-back difference in viscosity increased with increasing volume of lidocaine, suggesting that larger volumes of lidocaine required more mixing than small volumes, but also reflecting a greater magnitude of change in physical properties with increasing concentration of lidocaine. Profiles of the extrusion force versus syringe extension also demonstrated that 10 mixing strokes were adequate to homogeneously mix the CHM and lidocaine solution (Figure 3).

Following 10 mixing strokes, the extrusion force was uniform from the front to the back of the syringe, even at the maximum tested volume of lidocaine. In contrast, the front extrusion force was much lower than the back extrusion force for syringes blended with 2 or 5 mixing strokes, and the front of the syringe exhibited numerous jagged troughs, indicating the presence of air bubbles in the syringe.

2. Changes in Viscosity with Differing Concentrations of Lidocaine

Viscosities of CHM/lidocaine blends decreased with increasing lidocaine HCl. As shown in Figure 4, the dynamic viscosity of CHM/lidocaine blends was inversely proportional to the volume of lidocaine-HCl solution ($R^2 = 0.99$). Even at 0.23 mL of lidocaine HCl, the CMC gel was cohesive enough to suspend the particles for the 24-hour testing period (Figure 4).

3. Extrusion Forces of Lidocaine and CHM Blend, Compared to CHM Alone

The extrusion forces of CHM/lidocaine blends were lower than those of CHM alone (Figure 5). The extrusion force through a 27-gauge, 0.5-inch B-D needle was nearly constant around 5.3 pounds of force (lbf) for CHM blended with 0.05, 0.10, or 0.15 mL lidocaine-HCl, down from 6.0 lbf for CHM

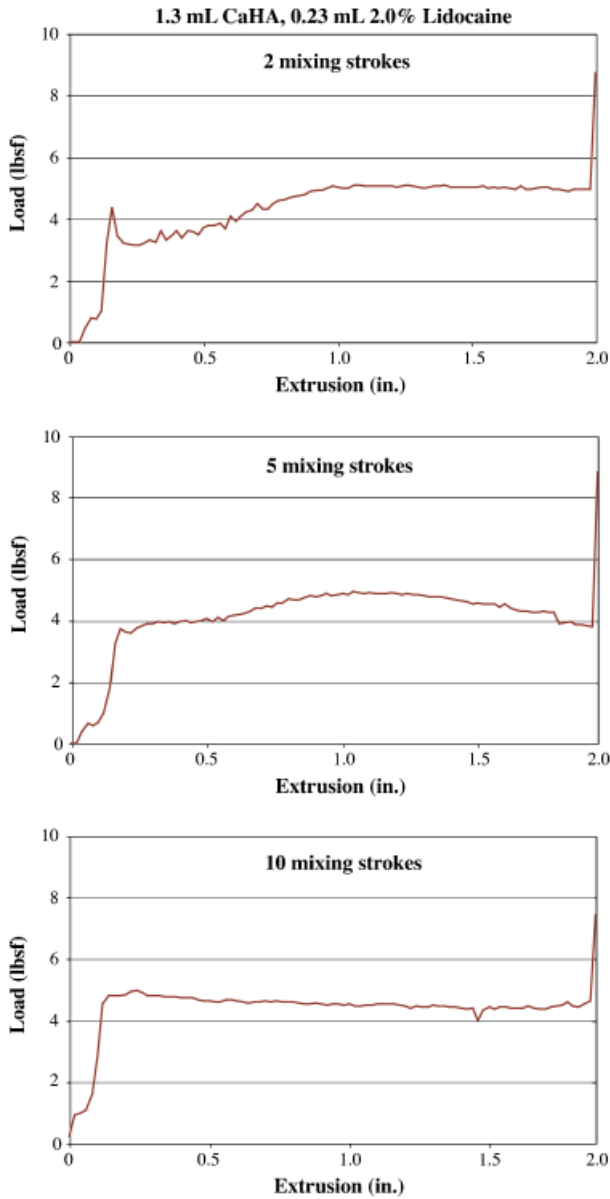


Figure 3. Force versus extension of CaHA with 0.23 mL lidocaine (0.3%).

alone. Extrusion force decreased to 4.7 lbf for 1.3 mL CHM with 0.23 mL 2% lidocaine solution.

4. Incidence of Needle Jamming in Lidocaine/CHM Blend

Blending CHM with lidocaine did not increase the incidence of needle jamming. Twelve extrusions were performed for each of the seventeen experimental

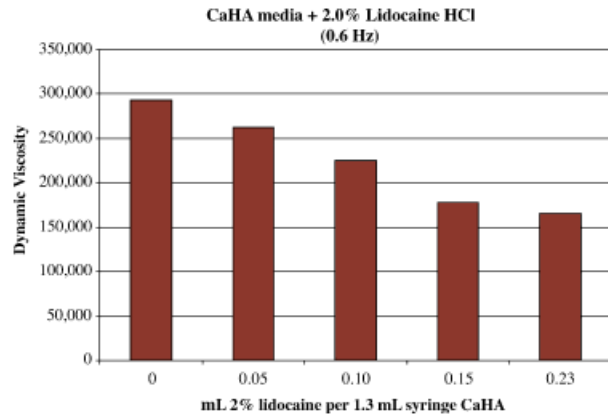


Figure 4. Dynamic viscosity of CHM blended with various volumes of 2% lidocaine-HCl.

conditions, for a total of 204 extrusions. Only two needle jams were observed among these extrusions, for an estimated jam rate of 0.98%. This jam rate is comparable to the jam rate observed for CHM.¹⁸

5. Elasticity and pH of Lidocaine/CHM Compared to CHM Alone

Elasticity is a qualitative term, while G' , G , and $\tan(\delta)$ are quantitative measures of how vigorously a material bounces back to its initial position following a stress or strain. The elasticity of CHM and lidocaine blends decreased with increasing concentration of lidocaine mixes (Figure 6). The $\tan \delta$ (δ) values (the tangent of the ratio of loss modulus $[G'']$ over the storage modulus $[G']$) provides a

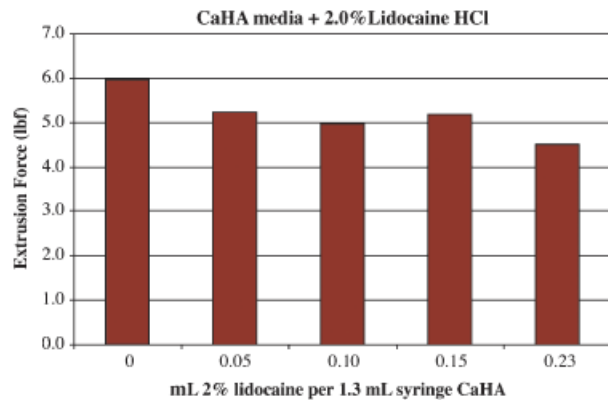


Figure 5. Extrusion force, CHM blended with various volumes of 2% lidocaine-HCl.

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