Controlled, Randomized Study of Pain Levels in Subjects Treated with Calcium Hydroxylapatite Premixed with Lidocaine for Correction of Nasolabial Folds

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BACKGROUND Calcium hydroxylapatite (CaHA) has been administered after nerve block injection of anesthetic agents.

OBJECTIVES This prospective, randomized, split-face, single-blind study (50 subjects) assessed the pain reduction, safety, and effectiveness of premixing CaHA with 2% lidocaine for the treatment of nasolabial folds (NLFs).

METHODS AND MATERIALS Subjects were randomized to receive treatment with CaHA alone in one NLF (control) and with CaHA premixed with lidocaine in the other NLF (treatment). Subjects completed pain assessments using a validated visual analog scale at specified time points immediately after injection, 1 hour after injection, and 1 month later. Subjects also indicated relative pain experience and preference assessments. Investigators completed aesthetic assessments at 2 weeks and 1 month. Subjects and investigators recorded adverse events.

RESULTS Subjects reported statistically significantly less pain in the treatment fold than in the control fold and expressed unanimous preference for the treatment injection over the control. Aesthetic results were essentially equivalent for both treatments.

CONCLUSION Investigators concluded that CaHA premixed with lidocaine results in significant pain reduction during dermal filler injection while maintaining the aesthetic improvement of CaHA without lidocaine and demonstrating comparable local transient adverse events for treatment and control.

BioForm Medical (San Mateo, CA) provided the soft tissue filler, lidocaine, and other necessary supplies used in this study. All authors are members of the Bioform Medical Education Faculty.

In clinical trials and commonly in regular clinical use, calcium hydroxylapatite (CaHA; Radiesse, BioForm Medical, San Mateo, CA) has been administered after nerve block injection of some anesthetic agent, usually lidocaine. One published study has recently reported the use of CaHA mixed with lidocaine.[1] In that study, the authors reported how the mixture appeared to reduce subject discomfort considerably during hand rejuvenation. Other studies on the use of CaHA combined with lidocaine or with lidocaine and epinephrine for treatment of the aging hand have also confirmed the original report from Busso and Applebaum.[2–4] In addition, published in vitro experiments[5] indicate that, when Radiesse is mixed with 2% lidocaine, the mixture does not separate or settle for at least 24 hours after mixing. Moreover, the admixture is homogenous from the front to the back of the syringe after approximately 10 back-and-forth movements of CaHA to lidocaine and lidocaine to CaHA syringes.[5]

In contrast to anecdotal reports, published studies on treatment of the hand, and in vitro experiments, this controlled investigation of CaHA combined with

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lidocaine and injected together focused on one of the most common treatment areas in facial aesthetics: the nasolabial folds (NLFs). This report represents the first blinded, controlled comparison providing quantitative demonstration of the pain reduction of mixing CaHA with lidocaine.

Study Objective and End points

The purpose of this prospective, randomized, split-face, single-blind study in 50 adult subjects was to assess the pain reduction, safety, and effectiveness of CaHA premixed with 2% lidocaine during treatment of NLFs. The study compared subjects' pain levels after randomized treatment with CaHA premixed with 2% lidocaine in one NLF (treatment) and with CaHA only in the contralateral fold (control).

The two primary effectiveness study end points were:

- To compare subject pain in the treatment and control fold immediately after NLF treatment.
- To assess whether observed differences in subject pain between the treatment and control folds immediately after NLF treatment were clinically meaningful.

The secondary effectiveness study end points were:

- To compare subject pain in the treatment and control folds 15, 30, and 45 minutes; 1 hour; 2 weeks; and 1 month after NLF treatment.
- To assess aesthetic effectiveness 2 weeks and 1 month after NLF treatment.
- To assess subject preference favoring one treatment over the other.

Study Adherence

The clinical study was conducted in accordance with applicable laws, regulatory requirements, and good clinical practices. The protocol, procedures, and informed consent forms were submitted to and approved by the Food and Drug Administration and the institutional review board for each investigational site before the study was initiated. Written informed consent was obtained from each subject before enrollment in the study.

Methods and Materials

Subject Population

Fifty subjects were enrolled in this split-face study conducted between September 2008 and November 2008. Fitzpatrick skin type[6] categories I to VI, determined by investigators, were represented as follows: 15 subjects in category I, 13 subjects in category II, five subjects in category III, seven subjects in category IV, five subjects in category V, and five subjects in category VI (Table 1). The age range of the subjects was 29 to 81, with a mean age of 53. Forty-one of the subjects (82%) were female, and nine (18%) were male. Race classifications were as follows: 34 (68%) Caucasian, 10 (20%) African American, four (8%) Hispanic, and two (4%) Asian. All 50 subjects were included in all safety and effectiveness analyses.

Inclusion and Exclusion Criteria

All subjects were aged 18 and older, had approximately symmetrical NLFs, were candidates for NLF treatment, understood and agreed not to undergo other facial procedures in the lower half of the face during the course of the study, and agreed to the treatment schedule and follow-up visits.

TABLE 1. Fitzpatrick Skin Type Scale Used for Selection and Data Collection[6]

Fitzpatrick Scale Skin Type	*Description*
I	Burns easily, never tans
II	Burns easily, tans minimally
III	Burns moderately, tans moderately
IV	Burns minimally, tans moderately
V	Rarely burns, tans profusely
VI	Never burns, tans profusely

Subjects excluded from consideration were those who had received any neurotoxins in the lower half of the face in the previous 6 months; any hyaluronic acid, CaHA, or collagen injections in the lower half of the face within 18 months; poly-L-lactic acid, polymethylmethacrylate, silicone, or any other permanent filler in the lower half of the face; chronic or recurrent infection or inflammation that would preclude participation in the study; known bleeding disorder or medication likely to increase risk of bleeding; history of hypersensitivity to lidocaine or anesthetics of the amide type; history of anaphylaxis or multiple severe allergies; and type of treatment or procedures of the NLFs, including NLF surgery. Female subjects with child-bearing potential, subjects who had received any investigational product within 30 days before study commencement, and subjects in whom NLF were too severe to be corrected in one treatment session were also excluded.

Mixing Procedure

To prepare the CaHA–lidocaine mix, 0.2 mL of lidocaine hydrochloric acid (HCl) was drawn from a 50-mL multidose vial into the 3.0-mL sterile polypropylene mixing syringe fitted with a sterile 27-gauge, 0.5-inch needle. Excess air was removed, followed by removal of the needle. The lidocaine HCl mixing syringe was then firmly connected to a syringe of 1.3 mL of Radiesse Dermal Filler using the female-to-female Luer lock connector. The lidocaine HCl and Radiesse Dermal Filler were then mixed together by alternately depressing the plungers, first on the mixing syringe and then on the Radiesse Dermal Filler syringe for 10 mixing strokes. Each mixing stroke consisted of one complete compression of the mixing syringe plunger followed by one complete compression of the Radiesse Dermal Filler syringe plunger. Plungers were compressed firmly and quickly, at approximately two compressions per second. After mixing, the mixing syringe and Luer lock connector were removed. The syringe containing the lidocaine HCl and Radiesse Dermal Filler was then fixed with an injection needle in preparation for NLF treatment.

TABLE 2. Injection Volumes

Injection Volume, mL	*Treatment*	*Control*
Mean ± standard deviation	0.962 ± 0.298	0.962 ± 0.298
Minimum	0.300	0.300
Maximum	1.400	1.400
Mean difference	0.0650	
p-value	$<.05$	

Treatment

First, baseline photographs were taken, and demographic information was collected. Next, subjects were injected with CaHA premixed with lidocaine in one NLF and CaHA alone in the contralateral NLF in a single treatment session. Treatment order and treatment side were randomized. The subjects were blinded to the randomization assignment. Both folds were injected using a 27-gauge inner-diameter needle. Each NLF was treated until an optimal cosmetic result was achieved according to the judgment of the injecting physician (Table 2). The injecting physician was instructed not to comment on any treatment type during the injection procedure or during the pain evaluation period.

Pain Evaluation

Pain level was evaluated immediately upon completion of injection for each fold and every 15 minutes after that for 1 hour. The investigators were not blinded to which fold received CaHA treatment with lidocaine and which fold did not. In contrast, the patients were blinded to which fold was the treatment fold and which was the control fold. Patients reported pain scores on a 10-point visual analog scale (VAS) from 0 for no pain to 10 for very severe pain.[7,8] Subjects marked directly on the VAS to record their level of pain at 0, 15, 30, 45, and 60 minutes after injection for treatment and control folds. At the completion of the 1-hour VAS evaluation, the subject was asked whether one treatment was less painful than the other. If subjects answered yes to this question, they were asked whether the difference in pain levels was significant enough to

affect preference for the treatment in one fold over the treatment in another. No ice, compression, pain medication, or nonprotocol anesthesia was permitted until after the 1-hour VAS was recorded. At this time, ice, cool compresses, or other nonprotocol anesthesia was allowed as necessary. Subjects were provided with a 30-day take-home diary in which to record adverse events.

Follow-Up Visits

Subjects returned for follow-up visits at 2 weeks and at 1 month. At both visits, subjects provided a pain assessment of their NLFs using the VAS and an aesthetic assessment of their NLFs using the Global Aesthetic Improvement Scale (GAIS; Table 3).[9] At these visits, subjects also returned their take-home diaries. Any adverse events reported or observed by subjects or physicians were recorded. Follow-up photographs were also taken. Participation in the study ended at the 1-month follow-up visit.

Statistical Methods

The incidence, type, severity, duration, and timing of all local and systemic adverse events were reported. Overall adverse event rates were presented using exact 95% confidence intervals. A significant reduction in pain at time 0 was analyzed using a paired *t*-test to test the null hypothesis that the mean of the differences in VAS pain assessments between the treatment and control sides was 0. For the analysis of percentage of subjects with a minimum of 2 points' difference on the VAS pain scale at time 0, the percentage that favored lidocaine was determined. That percentage was compared with a null hypothesis of 50% using an exact binomial test. A longitudinal analysis of the VAS data was also performed by applying a repeated-measures analysis of variance with factors of time and treatment for each subject.

Investigators used their clinical expertise to determine GAIS assessment. Although the data were not officially blinded, the investigators deliberately refrained from chart review that would identify which fold received lidocaine with CaHA and which fold received only CaHA before the follow-up visits. For the GAIS assessment at 2 weeks and 1 month, the percentage of subjects for which the GAIS with outcome in the treatment fold was equal to or superior to the control fold was determined. The corresponding one-sided 97.5% confidence interval was also determined for this percentage. Statistical significance was considered using two-sided tests at $p < .05$.

TABLE 3. Global Aesthetic Improvement Scale Used by Investigators[9]

Rating	*Description*
Very much improved	Optimal cosmetic result was achieved for the implant in this subject.
Much improved	Marked improvement in appearance from initial condition, but not completely optimal for this subject. A touch-up would slightly improve the result.
Improved	Obvious improvement in appearance from the initial condition, but a touch-up or retreatment is indicated.
No change	The appearance is essentially the same as the original condition.
Worse	The appearance is worse than the original condition.

Results

Primary Effectiveness End points

The first primary effectiveness end point of the study was to compare the level of pain using the VAS in the treatment fold and the control fold immediately after injection (time 0). Mean VAS scores at time 0 showed that subjects experienced statistically significantly less pain in the treatment fold (Figure 1). Specifically, the mean VAS score was 2.8 in the treatment fold and 6.6 in the control fold ($p < .001$), a significant difference in favor of the treatment fold.

The second primary effectiveness end point of the study was to assess percentage of subjects in which

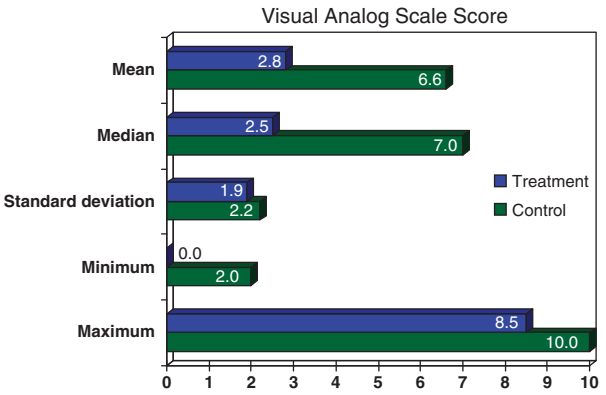

Figure 1. Visual analog scale at time 0.

there was a clinically meaningful difference in pain in the treatment fold at time 0. A clinically meaningful difference in pain was defined as at least a 2-point difference in pain on the VAS in the treatment and control folds. All subjects experienced at least 1 point less and 90% (45 of 50 subjects) at least 2 points less on the VAS for the treatment fold than for the control fold, demonstrating clinically meaningful less pain. The study protocol required that 70% of treatment folds show at least 2 points less on the VAS. Given that the lower bound on the confidence interval was 78.2%, the second primary effectiveness end point was also met ($p < .001$). In addition, no significant relationship was observed between patient-reported VAS scores and investigator-assessed Fitzpatrick skin type. (No group of patients with any one skin type reported more or less pain than groups of patients with any other skin type.)

Secondary Effectiveness End points

One of the secondary effectiveness end points of the study was to compare pain in the treatment and control folds at additional time intervals (15, 30, 45, and 60 minutes; 2 weeks; and 1 month) after NLF treatment. VAS pain scores at 15, 30, 45, and 60 minutes were statistically significantly lower in the treatment fold than in the control fold ($p < .001$). As expected, at 2 weeks and 1 month, there was no difference between the folds; pain ratings for both groups at those time points were 0 (no pain).

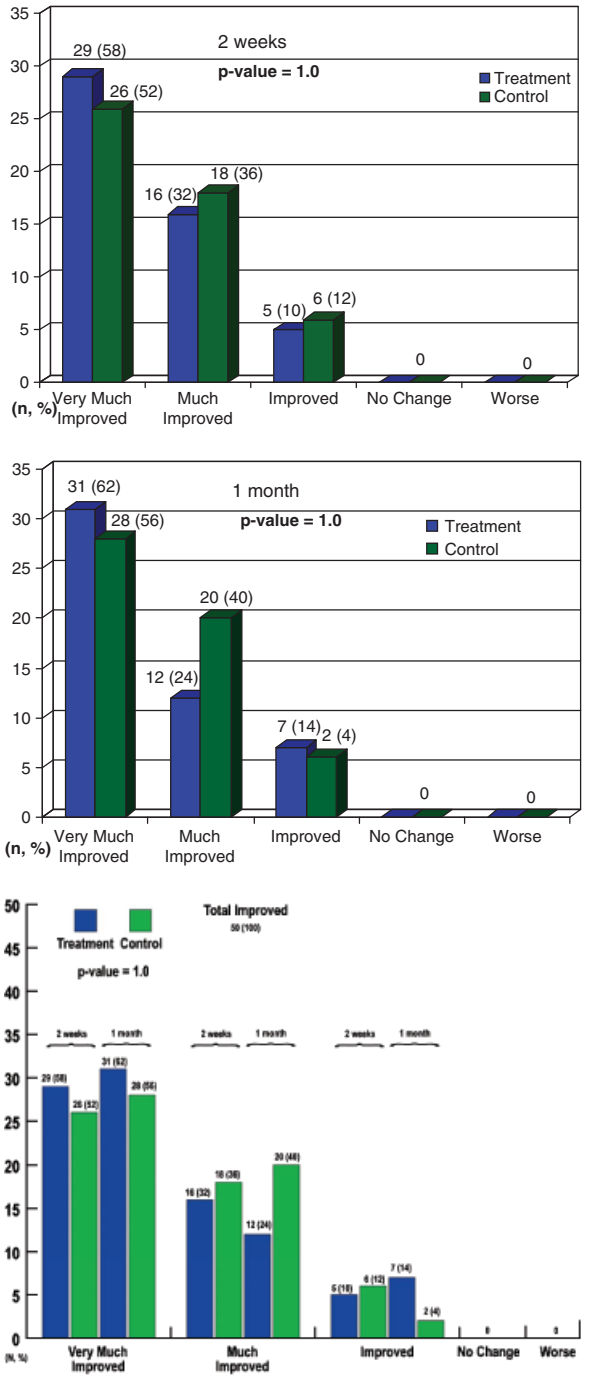

Figure 2. Investigator scores at 2 weeks and 1 month.

Another secondary effectiveness end point was to compare aesthetic improvement on the GAIS at 2 weeks and 1 month after treatment in the treatment and control folds. All subjects in both NLF groups were improved, much improved, or very much improved on the GAIS at 2 weeks and 1 month

TABLE 4. Adverse Events Reported in Subject Diaries

	Treatment	*Control*	p-*value*
Adverse Event	n		
Bruising	26	25	>.99
Itching	13	16	.16
Pain	22	25	.53
Redness	29	32	.48
Swelling	47	44	.48
Other	6	6	Not available

(Figure 2). Aesthetic assessment did not extend past the 1-month time period specified in the study protocol.

The third secondary effectiveness end point was to assess subject preference at the end of the 1-hour pain assessment. Blinded to treatment assignment, all 50 subjects indicated that one treatment was less painful than the other; 48 subjects (96%) indicated that the difference in pain level was pronounced enough to affect their preference for one treatment over the other. All 48 of the patients indicating a preference preferred the CaHA mixed with lidocaine as the preferred treatment. The remaining two subjects (4%) had no preference.

Safety

Adverse events were reported in subject diaries and by the investigators, with the overwhelming majority of adverse events reported in the subject diaries. Investigators reported only two adverse events: generalized short-term depression unrelated to the study in one subject and redness in the control fold that resolved in 3 days in another subject. The most common events recorded in the subjects' diaries were bruising, itching, pain, redness, and swelling, all of which resolved within 7 days (Table 4). None of the recorded adverse events was statistically significant when the treatment fold was compared with the control fold. In addition, seven other adverse events were reported in subject diaries for the treatment and control folds. None of these diary events appeared serious to the investigator. For example, one subject reported tightness for 2 days in both folds, another subject reported bleeding for 1 day, and a third subject reported needle marks for 1 day. One of the subjects who reported tightness also complained of a lump on the left nostril for 1 day. Another subject reported a pimple and left nostril sensitivity for 4 days. In another subject, a crease from the lower lip down was noted for 3 days. One subject reported a small lump, which was ongoing in the diary.

Discussion

This study should provide quantifiable support for the decision to mix the dermal filler CaHA with an anesthetic before injection into the NLF. Sample size was sufficiently powered and the population sufficiently diverse to resolve doubts about concerns about race, sex, and age. Brevity of follow-up may be considered a limitation in this study, in particular regarding duration of efficacy past the 1-month period specified in the study protocol, but the primary end points of the study were assessment of pain at time 0 and then at points extending to 1 month. The investigators did not ask the subjects to return at later periods for aesthetic assessment.

Subject participation was considered complete at the 1-month visit. We relied on subject diaries and our professional assessments to tally the data that we found in that time period, but in our anecdotal conversations with the patients, we have heard no further reports that run counter to the findings presented in this article. Because prior published data support the longevity of the aesthetic effectiveness of CaHA, we did not lengthen the follow-up time points for that end point.[10]

We found clinically meaningful and statistically significant differences in the patients' pain level in the CaHA premixed with lidocaine and the CaHA alone. Moreover, patients, blinded to control and

treatment folds, rated the control fold as more than 2 times as painful as the treatment fold. Four patients rated no pain at all in the treatment fold.

Aesthetic results were essentially equivalent in the two groups, with no difference in clinical efficacy at 2 weeks and 1 month. In addition, there were no statistically significant differences in adverse events, and the events were generally minor and short in duration. This adverse event profile is consistent with findings experienced in most aesthetic environments. Minor adverse events tend to present shortly after injection and dissipate within days or a few weeks.

It would appear that the face and hands are suitable areas of application for this patient-friendly technique of injection of CaHA. Treatment times can probably be shortened with the premixing, and patient discomfort levels appear to be lower as well. We are confident that premixing of CaHA and lidocaine will become rapidly adopted and look forward to reading of other studies using this mixing treatment regimen.

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