Multinational, Multipatient Study of Calcium Hydroxylapatite for Treatment of the Aging Hand: European Cosmetic Physician Group on Hand Augmentation

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BACKGROUND The hand has until now presented multiple challenges to practitioners seeking to painlessly treat signs of aging.

OBJECTIVE In this six-country European study with 62 adult patients, investigators examined the efficacy of calcium hydroxylapatite (CaHA) combined with anesthetic to address diminished volume in the aging hand.

MATERIALS AND METHODS Physicians used one of two interdigital injection techniques: 0.1 mL of lidocaine bolus per hand followed by CaHA or 1.3 mL of CaHA premixed with 0.1 to 0.2 mL of lidocaine. Massage and molding to distribute the filler followed injection. Patients were seen at three intervals over 12 weeks.

RESULTS Final results showed that 86% of patients were satisfied or better on a 6-point scale. At week 12, investigators expressed high satisfaction, with a 93% satisfaction rating or better. At weeks 2 and 12, physicians evaluated 98% of patients as improved or better on the Global Aesthetic Improvement Scale. Mild adverse events generally resolved within 2 weeks. Three cases of delayed edema reported 7 to 14 days after treatment resolved without intervention.

CONCLUSION Ease of use, minimal postprocedure events, desirable cosmetic outcome, and duration underscore the benefits of CaHA as a safe, efficient, noninvasive treatment option for the aging hand.

BioForm Medical Europe commissioned this study and the attendant postmarketing surveillance. BioForm Medical Europe reimbursed each physician a designated sum for each completed patient treatment, including five sets of questionnaires and photos. In return for their participation and completion of the Media Release Form, patients received a maximum of three syringes of BioForm Medical product for treatment of the hands. The individual treating physician determined total cost of treatment.

It is not hyperbole to say that dermal fillers have revolutionized the facial aesthetic industry. Noninvasive and affordable, soft tissue filler enhancement now appeals to the growing population of baby boomers seeking to reverse the signs of aging, to patients suffering facial injury or human immunodeficiency virus (HIV)-associated lipoatrophy, and to practitioners, who can now administer soft tissue fillers—collagens, the hyaluronic acid compounds, poly-L-lactic acid (PLLA), and calcium hydroxylapatite (CaHA)—with minimal inconvenience to the patient.

The face is but one visible manifestation of the aging process. As the body matures, the hands suffer a loss of dorsal subcutaneous tissue, amplifying the tendons and veins and belying even the most flawlessly executed facial rejuvenation. Volume loss in the hand has been traditionally treated with mesotherapy, autologous fat replacement (grafting), or—

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ISSN: 1076-0512 • Dermatol Surg 2010;36:782–789 • DOI: 10.1111/j.1524-4725.2010.01548.x

more recently—permanent or longer-lasting injectable dermal fillers.[1] Mesotherapy generally employs multiple injections of low-viscosity, high-volume hyaluronic acid (HA) performed during a series of office visits.[1] Side effects can be bothersome. The diminished viscosity of the medium challenges precise needle placement in the thin surface layer of the hand; at the same time, the multiple injections may produce ecchymosis and edema.

Autologous fat transfer, or fat grafting, is a costly, invasive surgical technique in which fat is harvested from a donor site using liposuction with a relatively large bore needle and a liposuction cannula. Autologous fat transfer may require multiple treatments, and longevity is not easily predicted. In addition, it is often accompanied by post-treatment bruising and swelling.

Permanent fillers—polymethylmethacrylate, polyacrylamide, and silicone—may offer sufficiently long-lasting results, but these products do not naturally adjust to the aging tissue around the area of implantation and are not often used because of the risk of long-term sequelae. Unlike permanent fillers, longer-lasting injectable dermal fillers such as PLLA and CaHA offer no visible contrast to the juxtaposing skin.[2] Use of PLLA in the hands requires multiple treatment sessions for desired effect, which can be costly to the patient. Furthermore, small, palpable nodule development reported in the face may pose problems in the hands as well, due to the thin overlying skin and tissues of the dorsal hand.[3,4] Because of its safety record with use in the face and its immediate and long-lasting results seen after injection, investigators sought to determine whether CaHA would be a viable alternative to other dermal filler products for treatment of the aging hand.

This article details a controlled study in which CaHA (Radiesse dermal filler, BioForm Medical, San Mateo, CA), a biocompatible, viscous, long-lasting resorbable soft tissue filler, was administered in a single treatment to augment thinning tissue of the aging hand.

Calcium Hydroxylapatite

In recent years, doctors have successfully treated the loss of hand volume with CaHA, a CE (*Conformité Européenne*)-approved (class III) injectable dermal filler consisting of CaHA microspheres (25–45 μm) suspended in an aqueous gel containing purified water, glycerin, and sodium carboxymethylcellulose, in a 30% microspheres to 70% carrier gel composition.[5] Storable at room temperature for up to 2 years, CaHA is supplied in 1.5-, 1.3-, 0.8-, and 0.3-mL prefilled syringes. Microspheres in the filler stimulate collagenesis, resulting over time in the growth of collagen in and around the microspheres of CaHA.[6]

Malleable, moderately viscous, and easily distributed throughout the hand with gentle massaging, CaHA is biocompatible and gradually absorbed by the body. It has received approvals in Europe for "plastic and reconstructive surgery, including deep dermal and sub-dermal soft tissue augmentation of the facial area," and for vocal fold medialization and vocal fold insufficiency that may be improved by injection of a soft tissue bulking agent. In the United States, CaHA has been approved for facial soft-tissue augmentation and the correction of HIV-related facial wasting, vocal fold augmentation, radiographic tissue marking, and oral–maxillofacial applications.

CaHA can be combined before injection with a local anesthetic and administered in a single treatment, resulting in a nearly pain-free treatment without the use of additional anesthesia such as nerve blocks or topical agents.[7,8] Cosmetic enhancement is immediate and typically lasts approximately 1 year.[9] Post-treatment effects may include edema, erythema, and bruising[10] requiring minimal self-care and limited follow-up office visits.

Materials and Methods

Patient Population and Enrollment Procedures

In this 22-physician study, 62 subjects, 1 man and 61 women from six European countries, were

TABLE 1. Patients and Physicians Per Country in Six-Country Study (Belgium and The Netherlands Reported Together)

	n				
	France	*Germany*	*Belgium and The Netherlands*	*Spain*	*United Kingdom*
Patients	12	6	12	23	9
Physicians	5	2	4	8	3

enrolled in a 12-week outpatient observational study to determine the efficacy, safety, and required volume of CaHA for augmentation and rejuvenation of the dorsal side of the hands (Table 1). Each of the investigators treated two to three subjects with CaHA. All patients met the minimum age requirement of 18 and presented with treatable volume loss on the hands. Subjects were required to sign consent and release forms and to appear for one initial treatment visit and two evaluative follow-up visits during week 2 ($\pm$ 7 days) and week 12 ($\pm$ 7 days) (Table 1).

Patient enrollment began in September 2008 and ended in November 2008. Each patient was monitored for 12 weeks, ending in February 2009. Exclusion criteria included any condition contraindicated in the labeling for CaHA (e.g., prior dermal filler injections at the treatment site, keloidal scarring, acute or chronic infections near the injection site, bleeding disorders, collagen disease); disqualification by the treating physician; previous permanent soft tissue filler or PLLA treatment on the dorsal aspect of the hands; treatment of the same area with a hyaluronic acid–based dermal filler in the preceding 6 months; known hypersensitivity to lidocaine or other topical or local anesthetic, to CaHA, or to one of its components; a preexisting condition; or routinely administered medication that would preclude use of a dermal filler.

After an explanation of the study, procedures, inclusion and exclusion criteria, and follow-up protocol, a written informed consent and signed media release form were obtained from each subject.

Treatment Protocol

One of two treatment techniques was selected to be used, according to the discretion of each physician. In each treatment, administration of a local anesthetic in conjunction with or preceding the dermal filler was involved. Patients' hands were first cleaned with alcohol or another antiseptic solution. Before administering the product, the dorsal skin of each treated hand was lifted between the practitioner's thumb and index finger to separate the tissue from the underlying veins and tendons and expose the potential space between the skin and fascia overlying the hand musculature. The needle (0.75-inch or 1.25-inch, depending on physician preference) was inserted at a 45° angle at each treatment site, and material was injected subdermally into the potential space until a bolus of product was formed. Light massage was used to distribute the material evenly into the patients' hands. At the discretion of the physician, patients were treated with ice packs to alleviate post-treatment swelling and bruising.

Technique 1 (Alternating Bolus Injections with Lidocaine and CaHA): In Technique 1, 0.1-mL boluses of 0.1% or 0.2% lidocaine were injected interdigitally, using a 27-gauge needle, into the areas of the first hand where CaHA was to be placed. CaHA was then injected into these same areas. The procedures were repeated for the second hand. The treating physician determined product volume.

Technique 2 (Premixed Combination of Lidocaine and CaHA): To create an admixture of local anesthetic and dermal filler, a 2- or 3-mL syringe containing 0.1 to 0.2 mL of lidocaine (1–2%) was introduced into a syringe containing 1.3 mL of

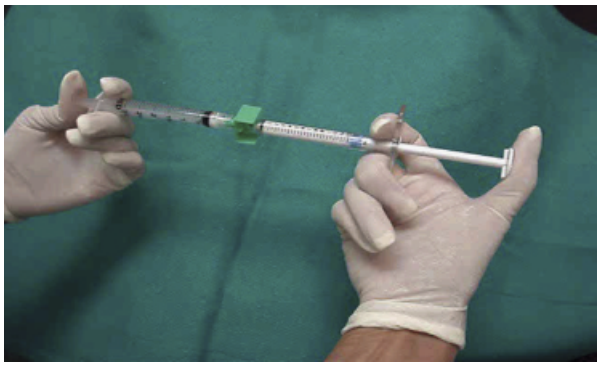

Figure 1. Admixture of local anesthetic and dermal filler—a 2- or 3-mL syringe containing 0.1 to 0.2 mL of lidocaine (1–2%) introduced to a syringe containing 1.3 mL of calcium hydroxylapatite.

CaHA through a Rapid Fill Luer-Lok-to-Luer-Lok (Baxa, Englewood, CO) connector. The practitioner pushed the plunger of the CaHA syringe into the lidocaine syringe and continued the push-pull action between syringes to create a homogeneous mixture of filler and anesthetic (optimal results require 10 "passes" between syringes) (Figure 1).[6,9] The syringe containing the CaHA was then disconnected from the other syringe. The CaHA and lidocaine mixture was injected interdigitally using a 27-gauge needle at the subdermal level as in Technique 1 (Figure 1).

After injection, the physician massaged the filler into the patient's loose-fisted hand to evenly distribute the material and achieve the desired cosmetic effect.

Baseline digital photographs were taken immediately before and after treatment and at each of the two follow-up visits, for a total of five photographs. On the first day of treatment, photo 1 was taken of both pretreated hands. Photo 2 was taken of both hands after treatment of the left hand. Photo 3 was taken of both hands after treatment of the right hand. At weeks 2 and 12, photos 4 and 5 were taken of both hands. To ensure standardization, instructions detailing photographic conditions, lighting, required background, and position of the hands were provided to physicians.

At the end of each visit, patients and physicians completed satisfaction assessment forms and were given the opportunity to evaluate their response to treatment outcome as very satisfied, satisfied, moderately satisfied, moderately unsatisfied, unsatisfied, or very unsatisfied. At the top of the physician's form was a space in which to record the volume of dermal filler injected into each patient's hand. Patients were examined for adverse events, which, if applicable, the physician recorded. At weeks 2 and 12, physicians charted patient progress on the Global Aesthetic Improvement Scale (GAIS), assessing change as very much improved, much improved, improved, no change, or worse.[11]

Results

Cosmetic Results

The end point of the study was treatment to full correction, as determined by the participating investigators themselves in their respective clinics. Only one treatment session was performed in each of the 62 enrolled patients, during which the right and left hands were injected with a combined total volume of CaHA for both hands ranging from 0.80 to 5.20 mL. Mean volume in the left hand was 1.48 mL; mean volume in the right hand was 1.5 mL, shown as total mean volume in Figure 2. The number of injection sites varied according to the requirement of full correction, with the number of injection sites per

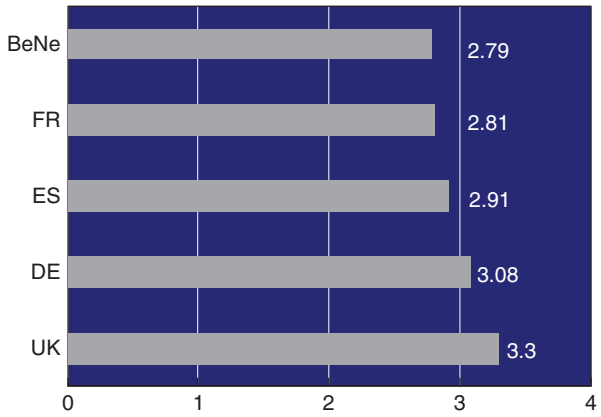

Figure 2. Mean mL volumes per country (Belgium and The Netherlands reported together).

hand ranging from 1 to 4 (into each possible interdigital space). Records were not accessible for mean number of sites, but conversations with investigators suggest that the mean number of injections per hand was approximately 3. Volume of product administered depended on the degree of tissue loss and the amount of filler that the individual physician deemed necessary to restore youthful contour. No patients received follow-up injections as part of the treatment protocol. The mean total volume administered in the United Kingdom was slightly higher (> 0.4 mL) than in the continental European countries (Figure 2).

Adverse Events

Physicians reported unusual incidents or adverse events related to the injections, material, or equipment for each visit. No serious adverse events were reported during the study. Physician-evaluated events were mild, temporary, expected, and of similar duration, severity, and type, including edema ($n = 4$), delayed edema ($n = 3$), erythema ($n = 2$), tenderness ($n = 3$), and pain ($n = 4$). The three cases of delayed edema, each administered by separate physicians, appeared at 7, 10, and 14 days and resolved on their own. Some instances of bruising were reported resulting from vascular damage or irritation near the injection site. In some cases, one or more of these conditions appeared in the same individual. No physician investigators reported the presence of lumpiness or bumps in treated hands.

Physician and Patient Average Satisfaction Ratings

Investigators obtained data immediately after treatment, then at 2 weeks, and again at 12 weeks.

Initial Visit

After the procedure, 93% of patients and 90% of physicians stated that they felt satisfied or better with the treatment. One physician reported being moderately unsatisfied because of injection technique, and another physician reported very unsatisfied for one patient but then reported very satisfied at the next visit. The very unsatisfied rating arose from an inadvertent hematoma that lead to ecchymosis and edema, both of which resolved by the 2-week visit.

Two-Week Follow-Up

At 2 weeks, 88% of patients and 90% of physicians reported satisfied or better (Table 2). Physicians rated 98% of the patients as improved or better on the GAIS.

Twelve-Week Follow-Up

At 12 weeks, 86% of patients and 93% of physicians reported satisfied or better. Physicians evaluated 98% of the patients as improved or better on the GAIS.

Figures 3 to 6 are representative before-and-after photos of sample subjects from three countries at various intervals throughout the study period.

In Figure 3, the patient received 1.3 mL of CaHA in each hand, for a total of 2.6 mL of CaHA. Post-treatment photos were taken after 3 weeks.

In Figure 4, the patient received 1.95 mL of CaHA in each hand, for a total of 3.90 mL of CaHA. Post-treatment photos were taken immediately after treatment (left hand) and after 12 weeks.

In Figure 5, the patient received 1.3 mL of CaHA in in the left hand only for a total of 2.60 mL of CaHA. Post-treatment photos were taken immediately after the treatment.

TABLE 2. Patient and Physician Ratings of Satisfied or Better

	%		
	After Treatment	*Week 2*	*Week 12*
Physicians	90	90	93
Patients	93	88	86

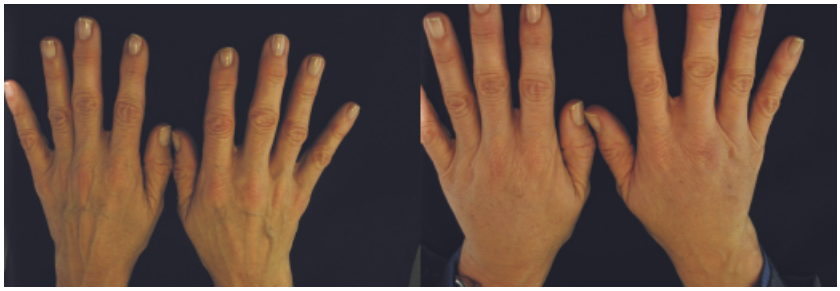

Figure 3. Patient received 1.3 mL of calcium hydroxylapatite (CaHA) in each hand, for a total of 2.6 mL of CaHA. Pretreatment photos on left; post-treatment photos on right were taken after 3 weeks (Dr. M. Baspeyras, Bordeaux, France).

In Figure 6, patient received 1.3 mL of CaHA in each hand, for a total of 2.6 mL of CaHA. Post-treatment photos were taken before and at 2 and 12 weeks.

Conclusion

Advances in materials, technology, and methodology have transformed and popularized the injection of soft tissue fillers as a practical, safe, and effective protocol for restoring lost volume to the face. No longer an unaffordable option, soft tissue facial augmentation can now be achieved with minimal to no discomfort or adverse events, often in one outpatient treatment.

Equally vulnerable to signs of aging are the hands. Exposed to the sun, climatic elements, and the wear and tear of daily living, the hands are especially vulnerable to the passage of time. Underlying veins and tendons become more pronounced as the skin loses volume because of the loss of subcutaneous tissue.

This study was undertaken to evaluate the efficacy, safety, and corrective value of CaHA for treatment of the aging hand. CaHA was administered with separate or simultaneous injections of local anesthetic, producing immediate results with no allergic reactions or serious adverse events in qualified subjects. Researchers could not determine the incidence of side effects with separate anesthetic versus simultaneous CaHA and anesthetic injections treatment because the data were not reported according to type of treatment. As a corollary, data about patient satisfaction for one treatment protocol rather

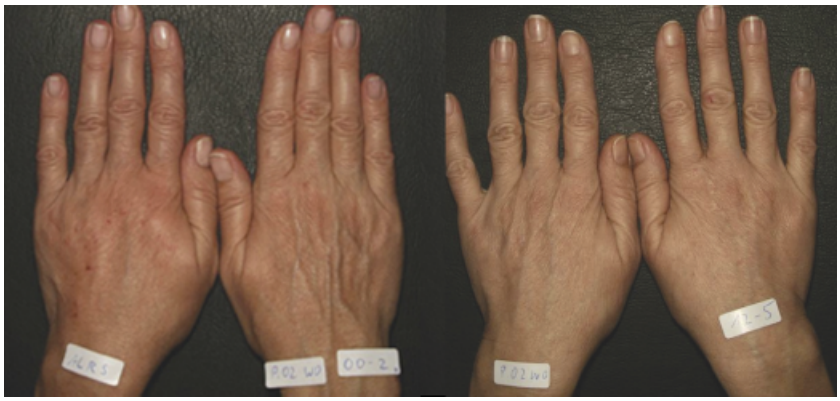

Figure 4. Patient received 1.95 mL of calcium hydroxyapatite (CaHA) in each hand, for a total of 3.90 mL of CaHA (right-sided photo indicates both treated hands at 12 weeks). Post-treatment photos were also taken immediately after treatment initially, direct comparison of the left and right hands are shown (far left photo, left hand [treated] versus the adjacent right hand [untreated]) (Dr. Storck, Munich, Germany).

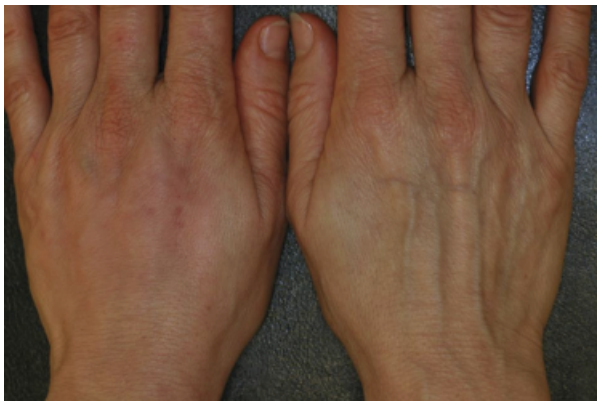

Figure 5. Patient received 1.3 mL of calcium hydroxylapatite in the left hand only. Post-treatment photo was taken immediately after treatment (Dr. A. Thio, Amsterdam, The Netherlands).

than the other were also not reported and are consequently unavailable.

No participant required follow-up injections at the two postoperative visits (weeks 2 and 12). The study yielded high satisfaction levels among patients and physicians at each visit, with 98% of patients rated on the GAIS as improved or better at week 12. Investigating physicians acknowledge that the GAIS is a validated scale for evaluation of facial treatments but felt that the categories of the GAIS were applicable to evaluation of the hands as well. Evaluation was based on clinical expertise of the participating physician in the clinic. The three self-resolving cases of delayed edema may have been in part attributable to no systematic instructions having been given to the subjects to refrain from physical activity for a period of time after treatment.

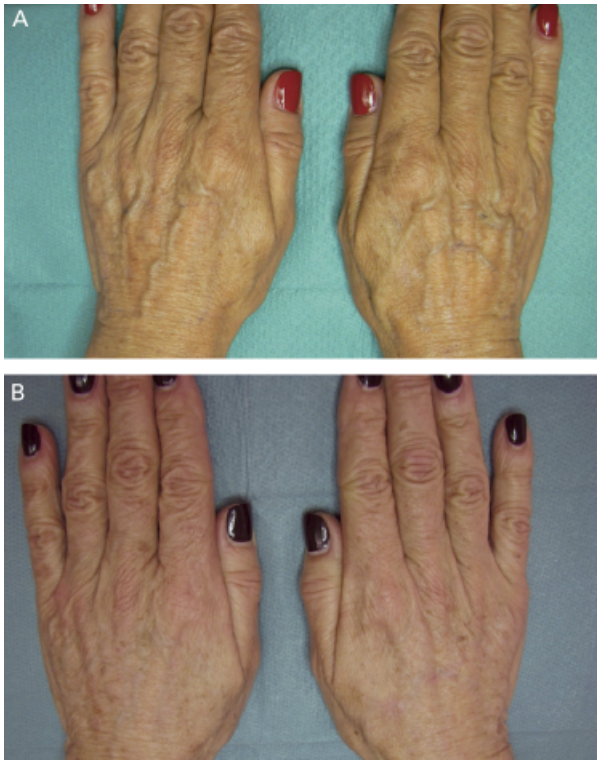

Figure 6. Patient received 1.3 mL of CaHA in each hand, for a total of 2.6 mL of calcium hydroxylapatite (CaHA). (A) Pre-treatment. (B) Post-treatment photos taken after 12 weeks (Dr. E. Essayagh, Antibes, France).

Radiesse is a noninvasive dermal filler that is easily administered in one outpatient visit. It is more viscous than the HAs, which appears to enhance its moldability in the face and hands, and it provides real-time, immediate results, in contrast to the multiple-treatment regimen necessary with PLLA. This study of CaHA suggests that the combination of time and minimum filler volume required for treatment may have an ameliorative effect on the cost of treatment for patients and practitioners. The time-to-volume ratio may even warrant a combined treatment price adjustment for hands and face that will probably improve economies of scale and encourage patient loyalty.

Acknowledgments The authors appreciate the assistance of David J. Howell, PhD, RRT (San Francisco), and Sally Sherwood, MA (New York City), in the development of this manuscript.

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