Complications from Nasolabial Fold Injection of Calcium Hydroxylapatite for Facial Soft-Tissue Augmentation: A Systematic Review and Meta-Analysis

Xiao-hua Shi, PhD; Xin Zhou, PhD; Yi-ming Zhang, MD; Ze-yuan Lei, MD; Ting Liu, PhD; and Dong-li Fan, MD

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Abstract

Background: Despite its increasing usage of facial applications, there is a paucity of objective data regarding calcium hydroxylapatite (CaHA).

Objectives: To systematically evaluate the complications from CaHA injection for facial soft tissue augmentation.

Methods: Published studies on CaHA injection for facial soft tissue enhancement were identified through searches of the PubMed, EMBASE, and Cochrane Controlled Trial databases. Only randomized, controlled trials comparing CaHA injection to either placebo or an active comparator for facial cosmetic use were included. The outcome measures were the count (n) and frequency (%) of each complication, including edema (swelling), erythema (redness), ecchymosis (bruising), pain, pruritus (itching), hematomas, nodules, and extrusions.

Results: Four studies on nasolabial fold (NLF) injection of CaHA consisting of two subgroups were included: (i) a CaHA-lidocaine vs CaHA subgroup and (ii) a CaHA vs hyaluronic acid (HA) subgroup. The addition of lidocaine to CaHA therapy displayed no significant effect on edema (RR (95% CI): 1.07 (0.94-1.21), P = .311), erythema (RR (95% CI): 0.91 (0.66-1.24), P = .544), ecchymosis (RR (95% CI): 1.04 (0.71-1.52), P = .843), pain (RR (95% CI): 0.88 (0.58-1.33), P = .553), or pruritus (RR (95% CI): 0.82 (0.45-1.50), P = .353). There was no significant difference between CaHA vs HA for hematomas (RR (95% CI): 0.24 (0.01-4.31), P = .332) or nodules (RR (95% CI): 0.18 (0.01-6.62), P = .353). There was no significant publication bias detected in either subgroup (Begg’s test P > .05).

Conclusions: These findings support the addition of lidocaine to NLF injection of CaHA and suggest an equivalence between CaHA and HA with respect to hematoma and nodule formation.

Level of Evidence: 2

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With age, facial skin loses its soft tissue fullness.1 To address this issue, physicians can augment tissue volume through injection of soft tissue fillers in the convenience of an office setting.1 Although soft filler substances have been experimented with for over a century, a new era in soft tissue fillers emerged in 1981 with the FDA approval of bovine collagen.1 Since that time, several soft tissue fillers have been introduced, including collagen, hyaluronic acid (HA), polymethylmethacrylate (PMMA), and autologous fat.1

Introduced in 2002, one such soft tissue filler — calcium hydroxylapatite (CaHA) — was initially used for oral and maxillofacial defects, vocal cord augmentation, and radiographic soft tissue marking.2 Having demonstrated a favorable safety profile, CaHA was then adopted for off-label facial

From the Department of Plastic and Cosmetic Surgery, Xinqiao Hospital, The Third Military Medical University, Chongqing, China.

Corresponding Author:
Dr Dong-li Fan, Department of Plastic and Cosmetic Surgery, Xinqiao Hospital, The Third Military Medical University, Chongqing 400037, P.R. China.
E-mail: donglifan1234@163.com
aesthetic indications. In December 2006, one CaHA product marketed as Radiesse by Bioform Medical (San Mateo, CA) received FDA approval for soft tissue augmentation. Specifically, Radiesse is an injectable soft-tissue filler composed of 25 to 45 µm microspheres of CaHA suspended in an aqueous sodium methylcellulose and glycerin gel carrier.

Despite its increasing usage for facial applications, there is a paucity of objective data regarding CaHA. A 2009 meta-analysis on patient satisfaction with CaHA for cosmetic nasolabial fold (NLF) correction conducted by Fakhre et al found that patient satisfaction was 4.16/5 at 3 to 6 months and 4.15/5 at one year. Although CaHA appears to have favorable long-term patient-centric outcomes, no systematic review and meta-analysis have yet analyzed the complications from CaHA injection for facial soft tissue enhancement. Therefore, the aim of this study will be to systematically evaluate the complications from CaHA injection for facial soft tissue augmentation.

METHODS
Search Criteria
This study was performed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Published studies on CaHA injection for facial soft tissue enhancement were identified through searches of the PubMed, EMBASE, and Cochrane Controlled Trial databases from inception to January 2015 (renewed April 2015). The search included the following terms: (hydroxylapatite OR CaHA OR Radiesse) AND facial AND random* AND control*.

Study Selection
This review only included data extracted from randomized, controlled trials (RCTs) comparing CaHA injection to either placebo or an active comparator for facial cosmetic use. Patients of all ages, either CaHA-naive or not, were considered. Any concomitant therapies were accepted, except when applied as exclusion criteria in the included studies.

Data Extraction and Outcome Measures
Data extraction was conducted independently by two co-authors, and any discrepancies between reviewers were resolved by discussion and consensus. For each study, we extracted the following information: first author’s name, year of publication, country, number of included patients in study, study arms (number in each arm), patient characteristics (mean age (and range), sex %), type of surgical procedure, CaHA dose, additional therapies and dose (if any), median follow-up period (days), percentage of protocol violations (%), and adverse event/side effects/complications (count (n) and frequency (%)), including edema (swelling), erythema (redness), ecchymosis (bruising), pain, pruritus (itching), hematomas, nodules, and extrusions.

The outcome measures were the count (n) and frequency (%) of each adverse event/side effect/complication. Therefore, efficacy was not part of the study selection, data extraction, or meta-analysis because the range of therapeutic indications and efficacy outcomes for CaHA are too diverse to pool.

Quality Assessment
A methodological quality assessment of the trials was performed using the methods reported by Jadad et al according to the following three parameters: (i) whether the trial reported an appropriate randomization method (0-2 scores); (ii) whether the trial reported an appropriate blinding method (0-2 scores); and (iii) whether the trial reported withdrawals and dropouts (0-1 scores). Therefore, the scoring ranged from 0 to 5 points, with “high-quality” defined as a score of at least three. This cutoff point of three was based on several previously published meta-analyses that have applied the Jadad scale.

Meta-Analysis
Characteristics of the included trials and adverse event/side effect/complication outcomes were extracted and entered into STATA (version 11.0; College Station, TX). Results of the intent to treat population were presented. Heterogeneity was identified using an I² statistic and chi-square-based Q-test (P < 0.05). An I² value exceeding 50% was deemed to represent significant heterogeneity. The dichotomous data were used to calculate relative risk (RR) estimates with 95% confidence intervals (CI) using a fixed effects model when significant heterogeneity was not detected (I² < 50%); otherwise, a random effects model was used. Studies were pooled and weighted according to the reciprocal of their variance, which was calculated as the square of the standard error (SE) provided in the individual trials. For the studies that assessed adverse event/side effect/complication outcomes but did not report them in either the CaHA or placebo/comparator treatment groups, non-zero approximations were entered into STATA. Publication bias was evaluated with Begg’s testing with P < 0.05 indicating statistically significant publication bias.

RESULTS
The flowchart of study selection is depicted in Figure 1. From a total of 45 records, four studies on NLF injection of CaHA were finally included in this meta-analysis. The characteristics of these studies are detailed in Table 1, and the findings from the Jadad methodological quality assessment are detailed in Table 2. The four included studies were divided into
two subgroups consisting of two studies each based on their treatment protocols: (i) a CaHA-lidocaine vs CaHA subgroup analysis and (ii) a CaHA vs HA subgroup analysis. The reported complications from the CaHA-lidocaine vs CaHA studies are detailed in Table 3 and those from the CaHA vs HA studies are detailed in Table 4.

On the basis of the reported data, the CaHA-lidocaine vs CaHA subgroup analysis allowed for five meta-analytical comparisons: edema (swelling), erythema (redness), ecchymosis (bruising), pain, and pruritus (itching). None of these displayed significant heterogeneity ($I^2 < 50\%$); therefore, a fixed effects model was used for all these comparisons. The addition of lidocaine to CaHA therapy displayed no significant effect upon edema (RR (95% CI): 1.07 (0.94-1.21), $P = .311$; Figure 2A), erythema (RR (95% CI): 0.91 (0.66-1.24), $P = .544$; Figure 2B), ecchymosis (RR (95% CI): 1.04 (0.71-1.52), $P = .843$; Figure 2C), pain (RR (95% CI): 0.88 (0.58-1.33), $P = .553$; Figure 2D), or pruritus (RR (95% CI): 0.82 (0.45-1.50), $P = .515$; Figure 2E). There was no significant publication bias detected in this subgroup (Begg’s test $P > 0.05$).

On the basis of the reported data, CaHA vs HA subgroup analysis allowed for two meta-analytical comparisons: hematomas and nodules. Both of these displayed significant heterogeneity ($I^2 > 50\%$); therefore, a random effects model was used for these two comparisons. There was no significant difference between CaHA vs hyaluronic acid (HA) for hematomas (RR (95% CI): 0.24 (0.01-4.31), $P = .332$; Figure 3A) or nodules (RR (95% CI): 0.18 (0.01-6.62), $P = .353$; Figure 3B). There was no significant publication bias detected in this subgroup (Begg’s test $P > 0.05$).

**Figure 1.** Flowchart of study selection.

**Table 1.** Characteristics of Included Studies

| Study and Year | Country       | No. of Patients | Mean age (Years) | Gender (F/M) | CaHA Mean Dose (mL, Range or SD) | Median Follow-up Period (Days) | Percentage of Protocol Violations (%) |
|---------------|---------------|-----------------|------------------|--------------|----------------------------------|---------------------------------|--------------------------------------|
| Grunebaum et al, 2010<sup>11</sup> | USA           | 16              | 57.8             | 15/1         | N/R                              | 144                             | 0%                                   |
| Marmur et al, 2010<sup>12</sup>   | USA           | 50              | 53               | 41/9         | 0.962 ± 0.298                    | 30                              | 0%                                   |
| Moers-Carpi et al, 2007<sup>13</sup> | Germany, Spain | 205             | 52               | 185/20       | 1.1-1.3 mL                       | 480                             | 6.34%                                |
| Moers-Carpi and Tufet, 2008<sup>14</sup> | Germany, Spain | 60              | 50.5             | 52/8         | 0.88 mL                          | 365                             | 0%                                   |

F, female; M, male; N/R, not reported; SD, standard deviation.

**Table 2.** Jadad Methodological Quality Assessment

| Study                          | Randomization 0-2 | Blinding 0-2 | Withdrawals or Dropouts 0-1 | Total Score |
|-------------------------------|------------------|--------------|----------------------------|-------------|
| Grunebaum et al, 2010<sup>11</sup> | 2                | 2            | 1                          | 5           |
| Marmur et al, 2010<sup>12</sup>   | 2                | 2            | 1                          | 5           |
| Moers-Carpi et al, 2007<sup>13</sup> | 2                | 2            | 0                          | 4           |
| Moers-Carpi and Tufet, 2008<sup>14</sup> | 2                | 2            | 1                          | 5           |
DISCUSSION

CaHA is a synthetic, non-animal derived filler product composed of naturally-occurring minerals found in bone and teeth.\textsuperscript{15} Since its FDA approval for correction of moderate to severe wrinkles and folds in 2006, CaHA has become a popular filler for facial volume restoration in the middle and lower face. A recent cadaveric study by Gatherwright et al that analyzed 3-dimensional changes in the midface and NLF volume, as well as lateral movement in the NLF/...
nasolabial crease (NLC) junction, revealed that malar CaHA injection provides a lifting effect accompanied by recruitment of ptotic tissue and lateral movement of the NLF-NLC junction. In vivo, CaHA has been shown to provide immediate volume replacement for up to one year followed by longer term correction due to in situ neocollagenesis, with the CaHA microspheres serving as scaffolding for new collagen fibrils. Eventually, the CaHA particles are degraded into their constituent calcium and phosphate ions and excreted through the urine. Due to this degradable, biocompatible property, CaHA is non-immunogenic and does not require skin testing.

In this study, we systematically evaluated the complications from NLF injection of CaHA for facial soft tissue augmentation. Based on the reported data, we were able to analyze two treatment modalities: CaHA-lidocaine vs CaHA and CaHA vs HA. First, although the addition of lidocaine to CaHA increases the filler’s malleability and molding ease while decreasing its viscosity and the extrusion force required, we found that the addition of lidocaine to CaHA therapy displayed no significant effect upon edema, erythema, ecchymosis, pain, or pruritus. Similarly, a previous 47-month safety study of CaHA by Sadick et al reported a mere seven minor events in a population of 113 patients, all of which resolved in 30 days. Second, we found no significant difference between CaHA and HA for hematomas or nodules. Similarly, a review by Emer et al that found a favorable safety profile for CaHA comparable to that of HA fillers.

There are several limitations to this study. First, due to the paucity of RCTs on this subject, there was a limited sample size with only four studies included in this meta-analysis. However, our findings are consistent with the accumulated clinical evidence. Second, on account of CaHA’s high viscosity and elasticity, clinical evidence contraindicates its use in mobile or unforgiving anatomical regions (eg, lips, glabella, or periocular regions) due to the risk of necrosis and nodule formation. Therefore, the current findings do not apply to these contraindicated uses. Third, this meta-analysis did not specifically address the use of CaHA in darker skin types, so the current findings cannot be applied to this patient subpopulation. That being said, Marmur et al’s 2009 study on darker skin types (ie, Fitzpatrick skin types IV to VI) revealed the absence of keloids, hypertrophic scarring, and hypopigmentation or hyperpigmentation three and six months after facial CaHA injection. Fourth, several case reports have described other, rarer types of complications arising from facial CaHA injection, such as inflammatory granulomatous reactions, eyelid masses (with and without ptosis), vascular occlusion, vascular embolization, skin necrosis, ischemic neuropathy, ocular ischemia, and idiopathic hemifacial atrophy. Although such complications were not included in the current meta-analysis, such rare complications are often not captured by RCTs due to insufficient powering and delayed events (ie, adverse events that present after the conclusion of the trial). Therefore, readers should be aware this meta-analysis does not provide exhaustive information on all the potential adverse effects of facial CaHA injection.

CONCLUSION

In conclusion, the addition of lidocaine to NLF injection of CaHA displayed no significant effect upon edema, erythema, ecchymosis, pain, or pruritus. Moreover, there was no significant difference between CaHA and HA for hematomas or nodules. These findings support the addition of lidocaine to NLF injection of CaHA in clinical practice and suggest an equivalence between CaHA and HA with respect to hematoma and nodule formation.

Disclosures

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**REFERENCES**

1. Murray CA, Zloty D, Warshawski L. The evolution of soft tissue fillers in clinical practice. *Dermatol Clin.* 2005;23(2):343-363.
2. Graivier MH, Bass LS, Busso M, Jasins ME, Narins RS, Tzikas TL. Calcium hydroxylapatite (Radiesse) for correction of the mid- and lower face: consensus recommendations. *Plast Reconstr Surg.* 2007;120(suppl 6):55S-66S.
3. Dayan SH, Bassichis BA. Facial dermal fillers: selection of appropriate products and techniques. *Aesthet Surg J.* 2008;28(3):336-347.
4. Fakhre GP, Perdikis G, Shadix KK, Terkonda SP, Waldorf JC. An evaluation of calcium hydroxylapatite (Radiesse) for cosmetic nasolabal fold correction: a meta-analysis and patient centric outcomes study. *Ann Plast Surg.* 2009;63(5):486-489.
5. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg.* 2010;8(5):336-341.
6. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials.* 1996;17(1):1-12.
7. Arroll B, Goodyear-Smith F. Corticosteroid injections for painful shoulder: a meta-analysis. *Br J Gen Pract.* 2005;55(512):224-228.
8. Bjordal JM, Johnson MI, Lopes-Martins RA, Bogen B, Chow R, Ljunggren AE. Short-term efficacy of physical interventions in osteoarthritis knee pain. A systematic review and meta-analysis of randomised placebo-controlled trials. *BMC Musculoskelet Disord.* 2007;8:51.
9. Purkayastha S, Tilney HS, Georgiou P, Athanasiou T, Tekkis PP, Darzi AW. Laparoscopic cholecystectomy versus mini-laparotomy cholecystectomy: a meta-analysis of randomised control trials. *Surg Endosc.* 2007;21(8):1294-1300.
10. Touray S, de Leeuw MA, Zuurmond WW, Perez RS. Psoas compartment block for lower extremity surgery: a meta-analysis. *Br J Anaesth.* 2008;101(6):750-760.
11. Grunebaum LD, Elsaie ML, Kaufman J. Six-month, double-blind, randomized, split-face study to compare the efficacy and safety of Calcium Hydroxylapatite (CaHA) mixed with Lidocaine and CaHA alone for correction of Nasolabal fold wrinkles. *Dermatol Surg.* 2010;36(suppl 1):760-765.
12. Marmur E, Green L, Busso M. Controlled, randomized study of pain levels in subjects treated with calcium hydroxylapatite premixed with lidocaine for correction of nasolabal folds. *Dermatol Surg.* 2010;36(3):309-315.
13. Moers-Carpi M, Vogt S, Santos BM, Planas J, Vallve SR, Howell DJ. A multicenter, randomized trial comparing calcium hydroxylapatite to two hyaluronic acids for treatment of nasolabal folds. *Dermatol Surg.* 2007;33(suppl 2):S144-S151.
14. Moers-Carpi MM, Tufet JO. Calcium hydroxylapatite versus nonanimal stabilized hyaluronic acid for the correction of nasolabal folds: a 12-month, multicenter, prospective, randomized, controlled, split-face trial. *Dermatol Surg.* 2008;34(2):210-215.
15. Emer J, Sundaram H. Aesthetic applications of calcium hydroxylapatite volumizing filler: an evidence-based review and discussion of current concepts: (part 1 of 2). *J Drugs Dermatol.* 2013;12(12):1345-1354.
16. Gatherwright JR, Brown MS, Katira KM, Rowe DJ. Three-dimensional changes in the midface following malar Calcium Hydroxylapatite injection in a cadaver model. *Aesthet Surg J.* 2015;35(6):NP169-NP175.
17. Kontis TC. Contemporary review of injectable facial fillers. *JAMA Facial Plast Surg.* 2013;15(1):58-64.
18. Chao YY, Chiu HH, Howell DJ. A novel injection technique for horizontal neck lines correction using calcium hydroxylapatite. *Dermatol Surg.* 2011;37(10):1542-1545.
19. Sadick NS, Katz BE, Roy D. A multicenter, 47-month study of safety and efficacy of calcium hydroxylapatite for soft tissue augmentation of nasolabal folds and other areas of the face. *Dermatol Surg.* 2007;33(suppl 2):S122-S126.
20. Marmur ES, Taylor SC, Grimes PE, Boyd CM, Porter JP, Yoo JY. Six-month safety results of calcium hydroxylapatite for treatment of nasolabal folds in Fitzpatrick skin types IV to VI. *Dermatol Surg.* 2009;35(suppl 2):1641-1645.
21. Sankar V, McGruff HS. Foreign body reaction to calcium hydroxylapatite after lip augmentation. *J Am Dent Assoc.* 2007;138(8):1093-1096.
22. Lee MJ, Sung MS, Kim NJ, Choung HK, Khwang SI. Eyelid mass secondary to injection of calcium hydroxylapatite facial filler. *Ophthal Plast Reconstr Surg.* 2008;24(5):421-423.
23. Beer K, Downie J, Beer J. A treatment protocol for vascular occlusion and ischemic optic neuropathy after facial calcium hydroxylapatite injection- a case report. *J Clin Aesthet Dermatol.* 2012;5(5):44-47.
24. Kao TE, Wu WC. Orbital ischemic oculomotor nerve palsy after vascular embolization from particulate soft tissue augmentation. *J Clin Aesthet Dermatol.* 2013;6(12):1345-1354.