

Use of Hyaluronidase in the Treatment of Granulomatous Hyaluronic Acid Reactions or Unwanted Hyaluronic Acid Misplacement

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BACKGROUND. In the past, reactions or misplacement of soft tissue fillers has been fraught with anxiety because time has been the main thrust for improvement in spite of ancillary treatments. Hyaluronidase is an enzyme that dissolves hyaluronic acid in the skin and also assists in the management of granulomatous foreign-body reactions to hyaluronic acid. These reactions may be caused by allergy to the material or immunologic response to the protein contaminants in the hyaluronic acid preparations. Dissolution of material in erroneous placement of material and in allergic reactions can be a time saver and a deterrent to patient dissatisfaction.

OBJECTIVE. To evaluate the use of hyaluronidase in the treatment of both allergic reactions and the erroneous misplacement of hyaluronic acid in the skin.

HAROLD J. BRODY, MD, HAS INDICATED NO SIGNIFICANT INTEREST WITH COMMERCIAL SUPPORTERS.

HYALURONIC ACID was approved for intracutaneous soft tissue administration in the United States in January 2004. Prior to introduction in the United States, reactivity to the products was variable. The protein load of the product was reformulated and reduced in 1999 and produced less reactivity on reintroduction.¹ I report a case of a reaction of longer than 5 months duration and the recalcitrance of management until hyaluronidase was used.

Hyaluronidase was also useful in the direct reduction of hyaluronic acid that was improperly placed during injection. I also report success with treatment for this indication.

Case 1

A 68-year-old female presented to our clinic for hyaluronic acid injections for wrinkles. She had received 26 bovine collagen injections over the previous 19 years without difficulty in the glabella and the oral commissures for peri-

METHODS. A case of persistent granulomatous reaction to injectable hyaluronic acid and a case of hyaluronic acid erroneous misplacement with their successful subsequent treatments using intracutaneous hyaluronidase are reported, along with illustrative examples of hyaluronidase use.

RESULTS. The use of hyaluronidase reduced the patient discomfort within 24 to 48 hours, deterring any patient anxiety or patient dissatisfaction.

CONCLUSIONS. Hyaluronidase has a place in the treatment of allergic reactions to hyaluronidase and in the erroneous misplacement of the material.

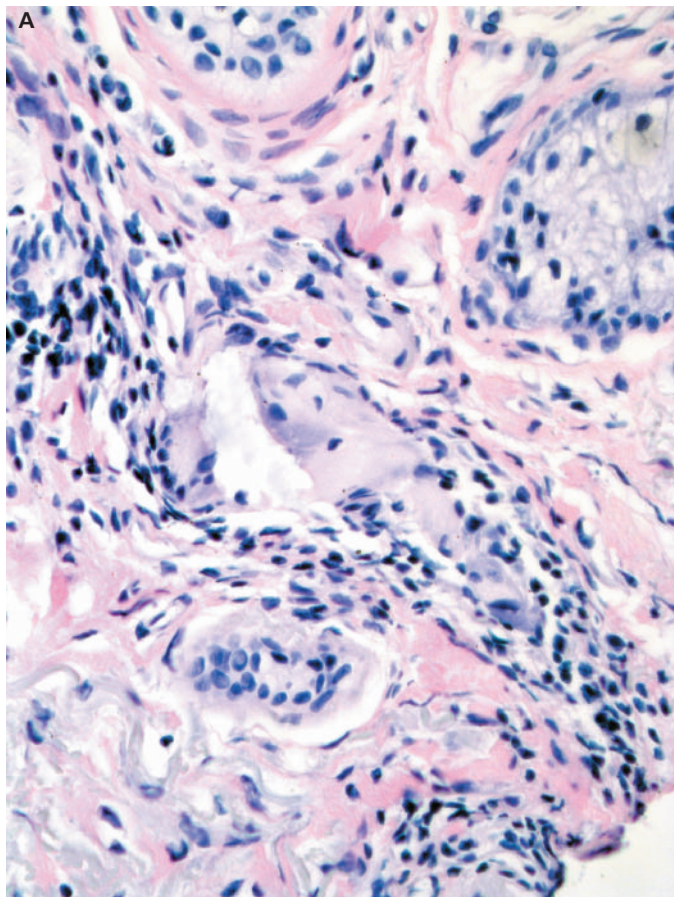
oral wrinkles. She was taking atorvastatin (Lipitor), alendronate (Fosamax), levothyroxine (Synthroid), and raloxifene (Evista) for hypercholesterolemia and osteoporosis. The patient received treatment around the mouth and in the commissures for the first time with non-animal-stabilized hyaluronic acid (NASHA) (Restylane, Medicis Pharmaceuticals, Scottsdale, AZ, USA) on May 2, 2004. She received additional bovine collagen (Zyplast and Zyderm II, Inamed Pharm.) layered over the hyaluronic acid and bovine collagen alone in the glabellar region. Within a week, the patient complained of redness, bumpiness, tenderness, and warmth in the chin and commissure area. On examination, she presented with multiple warm, red, indurated nodules in the area (Figure 1). Culture and sensitivity for aerobic and anaerobic bacteria were performed with drainage of clear fluid, which grew no organisms. Over the ensuing 3 weeks, she was injected with 3 mg/mL of triamcinolone acetonide, given antibiotics of cephalexin and trimethoprim-sulfisoxazole, and treated with multiple rapidly tapering weekly courses of prednisone, all of which seemed to have little sustaining effect. Continued application of desoximetasone cream, 0.25%, and tacrolimus ointment was of little benefit. A 2 mm punch biopsy performed a month later showed dermal fibrosis and chronic

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inflammation with focal granulomatous features. No organisms were identified on periodic acid–Schiff or acid-fast bacillus stains. Colloidal iron stains for mucin showed increased background staining but no specific foci of hyaluronic acid deposition (Figure 2).



Figure 1. Persistent nodular non-animal-stabilized hyaluronic acid (NASHA) reaction on the lower perioral area.



After 6 weeks, the reaction had subsided considerably, but several areas on the chin were still nodular and warm to the touch and would “go up and down” throughout the course of a day. The glabellar area that was injected with bovine collagen never produced any reactivity. The patient was improved 5 months after injection, but she still had a persistent nodule on the right side of her chin. An injection of hyaluronidase was prepared by diluting 0.5 cc of 150 units/cc (75 units) with 1.5 cc of 1% lidocaine with epinephrine (Table 1, source 3). This nodule was injected with 15 units (0.2 cc of a solution of 75 units) of hyaluronidase. Within 24 hours, the patient noted the disappearance of the nodule without recurrence.²

Case 2

A 64-year-old patient was seen in consultation regarding injection of NASHA injected into the immediate periorbital area below the lower cilia approximately 6 weeks prior to the visit. The material had been injected into the dermis and subcutis and was obvious as a pearly, contiguous, slightly blue, soft mass under each eye (Figure 3). The initial erythematous reaction after injection had taken almost 2 weeks to subside, but the material had not been

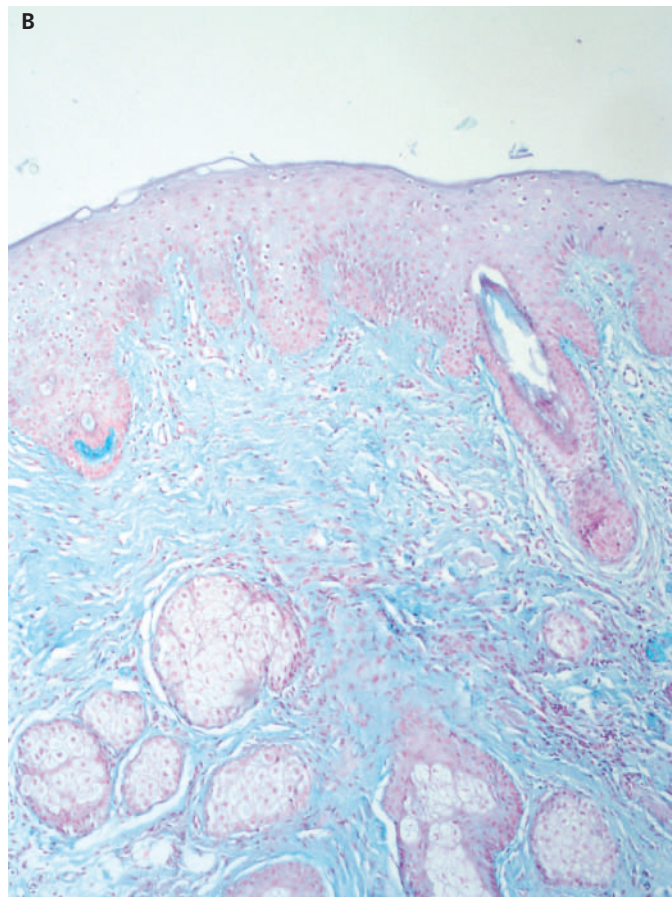


Figure 2. (A) Giant cell with dermal granulomatous reaction (hematoxylin-eosin stain; ×400 original magnification). (B) Colloidal iron stain showing background staining of glycosaminoglycans without focal deposition in the dermis (×100 original magnification).

reactive since then. An injection of 1 cc of 75 units of hyaluronidase (150 units/cc) combined with 1.5 cc of 1% lidocaine with epinephrine was done intradermally and subcutaneously under each eye. The patient experienced mild erythema, with disappearance of most of the material within 24 hours. (Figure 4). In 7 days, several small nodules remained and reinjection with 0.1 cc of hyaluronidase solution was accomplished. Mild ecchymosis occurred, along with dissolution of the remaining material within 5 days (Figure 5).

Case 3

A 45-year-old female had NASHA injected into significant nasolabial furrows, with good improvement. No signifi-

cant furrows were noted 8 weeks later. However, she noted that the left side of her nasolabial fold was larger than her right and that she thought that the material “moved over into the fold.” The fold was carefully injected with 0.5 cc of a solution of 75 units of hyaluronidase mixed with 1% lidocaine with epinephrine, sparing the area of the furrow. A slight erythema was noted within 24 hours, with little improvement of the area. It was discerned from previous pictures that the fold on her left side has always been slightly larger than that on her right side.

To clarify that hyaluronidase would be effective in dissolving both types of hyaluronic acid available for injection, a nurse volunteer was injected intradermally with 0.4 cc of NASHA filler in the right volar aspect of the forearm and 0.4 cc of avian hyaluronic acid (Hylaform, Inamed Pharm, Santa Barbara, CA, USA) into the left

Table 1. Sources of Hyaluronidase

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| <ol style="list-style-type: none">1. Amphadase (Amphastar Pharmaceuticals, Rancho Cucamonga, CA, USA): 150 units/mL of hyaluronidase, derived from bovine testicular tissue. Supplied in a 2 mL glass vial.2. Vitrase (Ista Pharmaceuticals, Inc., Irvine, CA, USA): 6,200 USP units of lyophilized dehydrated ovine hyaluronidase powder, nonpreserved in a single-use vial for reconstitution with 0.9% sodium chloride. Store unopened in refrigerator at 2–8°C. After reconstitution with saline, store at room temperature and use within 6 h. Addition of 6.2 mL of saline will yield 1,000 units/mL. If 0.075 mL of the reconstituted solution is added to 0.925 mL of sodium chloride, 75 units/mL will result. (Distributed by Allergan, Inc., Irvine, CA, USA, for ophthalmic use.)3. Hyaluronidase, 150 units/mL is available from Lee Pharmacy, Ft. Smith, AR, USA. Non-FDA-approved but FDA-registered bovine source, prepared under sterile conditions with bacterial, fungal, and pyrogenic potency testing confirmed by an FDA-registered laboratory. |
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FDA = US Food and Drug Administration.

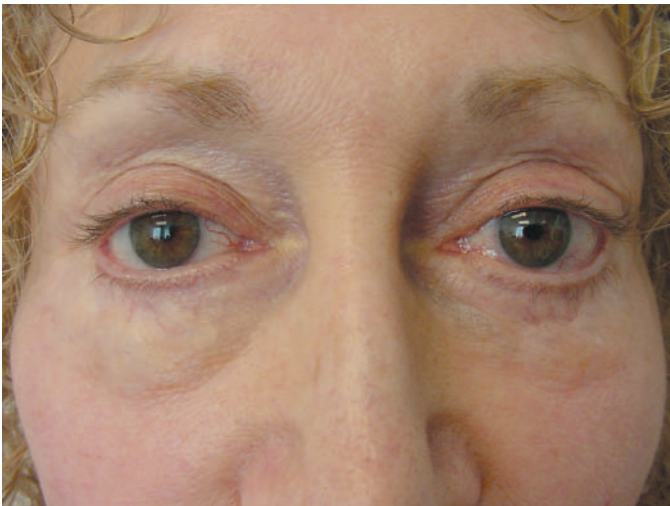


Figure 3. Erroneous placement of non-animal-stabilized hyaluronic acid (NASHA) under eyes 6 weeks after injection.

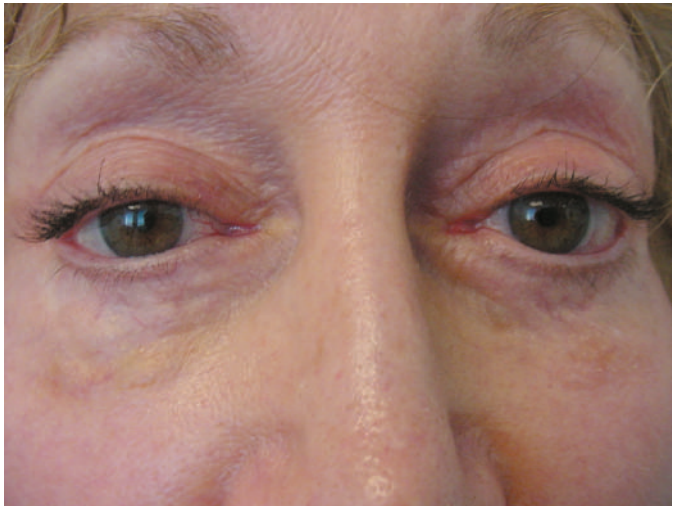


Figure 4. Twenty-four hours after hyaluronidase injection.



Figure 5. Five days after second injection of hyaluronidase (1 week after the first injection) with slight ecchymoses and resolution of improper placement of non-animal-stabilized hyaluronic acid (NASHA).

volar aspect of the forearm. In 1 week, the apparent nodules of hyaluronidase were injected with 0.2 cc of hyaluronidase in an undiluted concentration of 150 units/cc. One arm was injected and observed for reaction 10 minutes prior to injection of the other arm. Resolution of the nodules occurred without inflammation in 24 hours. No additional diluent was employed in these injections.

Discussion

Persistent reactions to temporary fillers have been fraught with problems.^{3,4} Nodularity within the reactions has produced unhappy patients, especially in those who have to face the public and show persistent lumpiness and especially in those who do not wish to wear makeup. Repetitive injectable cortisone or oral cortisone tapers, topical tacrolimus, and time have been the best treatment options. It is gratifying that hyaluronic acid is the only filler that can be reversed with a simple injection. Hyaluronidase injection represents an off-label use of a product approved by the US Food and Drug Administration (FDA).

The new release of hyaluronic acid in the United States has a sixfold reduction of protein load compared with the product released in Europe in the late 1990s.¹ In spite of this, I report a case of reactivity to NASHA (Restylane) persisting for 5 months. Klein hypothesized that allergy is not the chief cause of reactions to hyaluronic acid.¹ Studies suggest that immunoglobulin (Ig)G and IgE responses are rare and that most reactions are a response to protein contaminants rather than to hyaluronic acid itself. Excluding local injection-site reactions, the incidence of erythematous delayed-onset nonhypersensitivity reactions occurring 14 days or more after the last treatment with hyaluronic acid was 8.7% in Narins and colleagues' study of 138 patients, and they resolved within 2 to 3 months without treatment.⁵ True hypersensitivity reactions in the nature of case 1 were not formally evaluated but may be considered to have been present mixed with a group of unspecified persistent nodular reactions over 6 months with an incidence of 2.8%. Q-Med reported reactions in 2001 in Europe as 1 in 25,000 injections, with an adverse event rate of 0.03%.⁶ Lowe's experience with granulomatous reactions is 0.4%.⁷ Since the release of low-protein load hyaluronic acid in the United States, the incidence of reactivity has been estimated by Medicis Pharmaceuticals to be somewhere between 1 in 5,000 and 1 in 10,000, with an estimate of 1 in 8,500. This is based on European surveillance and represents unverified reactions lasting longer than 2 weeks (Dr. Mitchell Wortzman, Medicis Pharmaceuticals, personal communication, November 22, 2004). The reaction reported here in case 1 is a true hypersensitivity and granulomatous reaction, and it persisted for 5 months until treatment. There is a report from Canada of a patient with a similar episode of erythema, swelling, and

discomfort for up to 11 months after injection.⁸ In our practice, this case is unique and represents 1 in 690 injections over a period of 9 months, for an incidence of 0.14%. Most of the previous reactions reported have usually been self-limiting and resolved within 2 to 4 months. Whereas injection with cortisone and the use of tacrolimus were of minimal assistance, hyaluronidase can be very helpful to prevent reactions of longer duration.

Hyaluronidase is a soluble protein enzyme that acts at the site of local injection to break down and hydrolyze hyaluronic acid, a glucosaminoglycan polysaccharide in skin, connective tissue, and the vitreous humor of the eye. Tissue permeability is thereby increased.⁹ Hyaluronidase hydrolyzes hyaluronic acid by splitting the glucosaminidic bond between C1 of the glucosamine moiety and C4 of glucuronic acid. This temporarily decreases the viscosity of the intercellular cement, promotes diffusion of injected fluids, and facilitates the absorption of the fluid carrier, usually other drugs. Hyaluronidase causes more rapid spreading of subcutaneously injected agents and can be used in local anesthesia to increase the area affected, speeding the onset of anesthetic action in hypodermoclysis in infants. The rate of diffusion is proportional to the amount of enzyme, with the extent being proportionate to the volume of solution.¹⁰ Hyaluronidase was used in the early days of liposuction to try to augment the diffusion of epinephrine. This effect is not well documented under these circumstances. Hyaluronidase does not improve the anesthesia of the tumescent technique. It produces greater pain on subcutaneous infiltration while accelerating the rate of lidocaine absorption and therefore is not recommended.^{11,12}

Hyaluronidase is used in nerve block anesthesia and in retrobulbar anesthesia before ophthalmic surgery to increase the hypotonic effect of local anesthetics.¹³ It could be used to dissolve the commercial hyaluronic acid derived from cockscombs that is used for intra-articular injection to relieve pain from knee osteoarthritis. Sodium hyaluronate, the salt of hyaluronic acid, acts as a substitute for aqueous humor and is used by injection for cataract surgery and vitreous repair in ophthalmology.¹⁴ Hyaluronidase is also considered to be an antidote to the intravenous extravasations of chemotherapeutic vinca alkaloids or other irritating agents.

The reconstitution of the dermal barrier removed by intradermal injection of hyaluronidase indicates that the restoration of the barrier layer is complete in treated areas at 48 hours. At 24 hours, the restoration of the barrier is incomplete and inversely related to the dosage of enzyme. A dose of 0.02 units/mL would restore the dermal barrier more quickly than 2 units/mL, for example.⁶ This might encourage the dilution of the drug with saline or lidocaine in small doses of intradermal injection. In case 2, it is worthwhile to note that the use of epinephrine with lidocaine, with the hope of preventing bruising under the eye, was not effective during diffusion, in spite of holding pres-

sure after injection. No untoward effects were noted from diffusion of the epinephrine. Dilution with a small volume of saline or lidocaine should produce a more rapid resolution than full-strength hyaluronidase, although both would probably be roughly equivalent in the small doses administered here, as illustrated by the volar injection to the nurse forearms.

This soluble enzyme is prepared from mammalian testes, usually ovine or bovine. There is the potential for bovine pathogens and bovine spongiform encephalopathy if the material is illegally imported from outside the United States and locally compounded in unstandardized and under nonsterile conditions.

Adverse reactions are most frequently local injection-site reactions. Edema can occur in association with hypodermoclysis or dilution with local anesthetics. Hyaluronidase has also been reported to enhance the adverse events associated with coadministered drug products. It should not be used for insect bites or inflammation to avoid the spread of local infection. Urticaria and angioedema have been reported in less than 0.1% of patients and have occurred rarely after retrobulbar or intravenous injections.^{6,10}

Preliminary skin tests can be performed with ovine or bovine hyaluronidase using an intradermal injection of 0.02 mL (3 units) to observe local wheal and flare reaction within 5 minutes, constituting a positive reaction. Erythema or transient macular vasodilatation alone does not constitute a positive reaction.^{6,15} In the management of small areas of misplaced filler, 0.1 to 0.2 cc can be injected, as in the example of the nurse forearm injections, and carefully observed for 5 minutes before injecting other areas.

Patients receiving large doses of salicylates, cortisone, estrogens, or antihistamines may require larger doses of hyaluronidase for equivalent dispersing effect because these drugs render tissues partly resistant to the action of hyaluronidase. These drugs might have some applicability to cosmetic dermatologic surgery but only if wide areas are injected.

The availability of hyaluronidase has been limited since 2001 by Wyeth-Lederle Pharmaceutical's (Philadelphia, PA, USA) discontinuation of the bovine-derived Wydase because of fiscal concerns and the shutdown of a manufacturing plant.¹⁶ The recent availability of new FDA-approved forms of the drug coincides with the release of the newer forms of soft tissue hyaluronic acid fillers in dermatologic surgery (see Table 1). More concentrated forms of hyaluronic acid fillers are forthcoming for release

in the United States. If reactions occur or if the material is inadvertently injected in unwanted areas, there is little need for patient outrage or anxiety, especially in patients who rely on their appearance for their livelihood and cannot camouflage the reactions or nodularity. Prompt dissolution of the material or reduction of the reaction can usually be obtained with proper injection of hyaluronidase.

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