

Injected Hyaluronidase Reduces Restylane-Mediated Cutaneous Augmentation

A. John Vartanian, MD; Andrew S. Frankel, MD; Mark G. Rubin, MD

Objective: To determine the effects of injected hyaluronidase in cutaneous areas previously augmented with Restylane (Q-Med AB, Uppsala, Sweden), a nonanimal, stabilized hyaluronic acid (NASHA) gel.

Methods: A prospective, randomized study was undertaken in 2 parts. First, the effects of hyaluronidase and saline were compared on post-NASHA dermal augmentation. Next, 3 different doses of hyaluronidase were evaluated after NASHA gel dermal augmentation. A blinded evaluator assigned postinjection skin scores. Each patient served as his or her own control.

Results: Hyaluronidase dramatically reduced the size of the augmentation created by injected Restylane in all of our subjects. A comparison of average scores of saline-

injected sites vs hyaluronidase-injected sites revealed a statistically significant difference. By 4 to 7 days after hyaluronidase injection, skin scores were at 20% of baseline ($P < .001$). Dose-related response to injected hyaluronidase was also observed, although it was not statistically significant. A number of patients (25%) demonstrated localized, self-limiting hypersensitivity reactions to injected hyaluronidase.

Conclusions: Intradermal hyaluronidase injections can be used to reduce dermal augmentation from previously injected Restylane. A small dose of hyaluronidase equivalent to 5 to 10 U may be injected initially.

Arch Facial Plast Surg. 2005;7:231-237

RESTYLANE (Q-MED AB, Uppsala, Sweden), or nonanimal stabilized hyaluronic acid (NASHA) gel is approved by the United States Food and Drug Administration (FDA) for the filling of moderate to severe wrinkles around the nose and mouth, such as nasolabial folds. Restylane is a hyaluronic acid-containing gel produced by bacterial fermentation, stabilized by chemical cross-linking, and suspended in a physiologic buffer at a concentration of 20 mg/mL. When compared with bovine collagen, NASHA gel has demonstrated longer-lasting dermal augmentation results with significantly lower rates of hypersensitivity reactions.¹⁻⁴

As with any dermal filler, however, unintended dermal augmentation can occur with NASHA gel owing to overcorrection attempts or injection error. Given the long-lasting effects of NASHA gel injection, the resultant iatrogenic deformities could create persistent dissatisfaction in many patients. The key ingredient responsible for cutaneous augmentation with NASHA gel is hyaluronic acid, a natural,

high-viscosity hydrophilic mucopolysaccharide with an ability to hold water. Hyaluronidase is an enzyme that depolymerizes hyaluronic acid by cleavage of glycosidic bonds. It also breaks down other acid mucopolysaccharides found in connective tissue.⁵ Most surgeons are familiar with its use as a local anesthetic additive that facilitates cutaneous dissection via its enzymatic action on native hyaluronic acid found in the extracellular connective tissue matrix.^{6,7} We hypothesize that the enzymatic activity of hyaluronidase could also be used to accelerate the breakdown of hyaluronic acid in areas previously injected with NASHA gel.

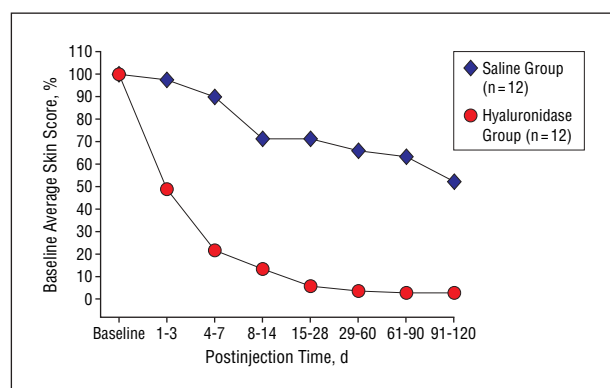
METHODS

Two prospective randomized studies were performed sequentially to determine the efficacy and dose dependency of hyaluronidase action on NASHA gel augmentation. Volunteers aged between 30 and 60 years participated in the study. Individuals with any significant medical histories, skin disorders, or previous allergies to hyaluronic acid products were excluded. Also excluded were patients who were

Author Affiliations:
Department of Otolaryngology–Head and Neck Surgery, University of Southern California, Los Angeles (Dr Vartanian); Department of Surgery, Division of Head and Neck Surgery, University of California, Los Angeles, UCLA School of Medicine (Drs Vartanian and Frankel); and Lasky Clinic (Dr Frankel) and Lasky Skin Clinic (Dr Rubin), Beverly Hills, Calif.

Table 1. Cutaneous Augmentation Grading Scale

Score	Cutaneous Manifestation
0	No trace of any injected material
1	Barely palpable or visible injection area
2	Slightly raised injection area "bump"
3	Moderately raised injection area
4	Significantly raised injection area

**Figure 1.** Average skin scores after saline vs hyaluronidase injections.

pregnant, nursing, or planning a pregnancy. No compensation was offered to enrolled subjects, and the study was financed entirely by us.

PART 1

In the first arm of the study, the effects of injected hyaluronidase or saline (its vehicle) on sites of previous NASHA gel injections were compared. Twelve subjects were enrolled in the study, each subject receiving 2 ipsilateral forearm injections of NASHA gel. Using a disposable 1-mL syringe with a Luer-lock needle hub, we injected 0.2-mL aliquots of NASHA gel intradermally at 2 ipsilateral forearm sites approximately 5 cm and 15 cm proximal to the wrist. A half-inch, 30-gauge needle was used for all NASHA gel injections. The skin was punctured once at each injection site to deliver the entire volume in 1 location. Fanning or tunneling types of injections were not used. Particular attention was directed at standardizing the depth of each injection to the level of the upper to middle dermis. To minimize the risk of bacterial contamination, the transfer of NASHA gel from the manufacturer-supplied vials to injection doses was done under sterile technique using a Luer lock-to-Luer lock transfer system (Byron Medical, Tucson, Ariz).

At 1 to 3 days after NASHA gel injection, each injection site was graded on a 5-point grading scale (**Table 1**). Each site was then randomly assigned to receive either 0.5 mL of 0.9% saline or 0.5 mL of hyaluronidase (150 U/mL, equivalent to 75 U of hyaluronidase). Post-NASHA gel injections were directed intradermally to the center of the raised lump. All injected hyaluronidase for all parts of this study was supplied by the same compounding pharmacy (Lee Pharmacy and Compounding Center; Fort Smith, Ark). Postinjections were delivered using the same syringe and needle hardware configuration as used for the initial NASHA gel injection.

The patients and the grading physician were blinded to the postinjection substance. The augmentation areas were each assigned a grade by the same blinded, noninjector examiner for

all evaluations. The subjects were examined on a regular basis for their response to the injections as well as for any adverse reactions. Skin palpation scores were assigned at 1 to 3 days after initial NASHA gel injection. Posthyaluronidase or post-saline injection scores were graded at days 1 to 3, 4 to 7, 8 to 14, 15 to 28, 29 to 60, 61 to 90, and 91 to 120 after injection with hyaluronidase or saline.

PART 2

The second part of the study was designed to evaluate the dose-dependent effects of injected hyaluronidase on NASHA gel augmentation sites. Eight volunteers were enrolled in the study. Each patient's left or right arm (randomly selected) received 3 individual injections of 0.2 mL of NASHA gel. The 3 injections were placed 5, 10, and 15 cm distal to the wrist on the randomly selected ipsilateral forearm. Syringe setup and injection depths were kept consistent, as in part 1 of the study. Three to 5 days later, each randomly selected NASHA gel injection site received an equal volume (0.4 mL) of 1 of 3 different concentrations of preservative-free hyaluronidase: 75 U/mL (equivalent to 30 U of hyaluronidase), 50 U/mL, (equivalent to 20 U of hyaluronidase), or 25 U/mL (equivalent to 10 U of hyaluronidase). The doses for each injection site were selected at random, and injection sites were then evaluated on a regular basis by the same (noninjecting) evaluator who was blinded to the concentration of hyaluronidase injected. Using the same palpation scoring scale as in part 1, we tracked the injected areas for the duration of the study. Grading and evaluation visits were also kept at the same interval as in part 1 of the study.

GRADING METHODS AND STATISTICAL ANALYSIS

A 5-point grading scale was used to assign injected sites a grade between 0 and 4 (**Table 1**). Grading was based on palpation scores assigned by a blinded examiner. A score of 4 was assigned to areas of maximal augmentation; 3 to areas that were moderately raised; 2 to a slightly raised bump; 1 to injection sites that were barely palpable at examination; and 0 to sites with no tactile trace of injected NASHA gel. In both parts of the study, statistical analysis was performed using a 1-way analysis of variance.

RESULTS

PART 1

Of the 12 volunteers who took part in the study, 7 (58%) were women. The age range of volunteers was between 30 and 60 years, with an average age of 43.7 and a median age of 44 years.

The injection of hyaluronidase after NASHA gel augmentation dramatically decreased skin scores. The most dramatic decline in palpation scores occurred between days 4 and 7 after hyaluronidase injection (**Figures 1, 2, and 3**). By the first week after postinjections, overall average skin scores in the hyaluronidase-injected group were about 20% of the baseline scores, while in the saline control group, the skin scores were at 90% of baseline. The decline in skin scores continued into the second week after hyaluronidase injection, leveling off by the third week. By the end of 14 days, the hyaluronidase group median skin scores declined to 0 while in the sa-

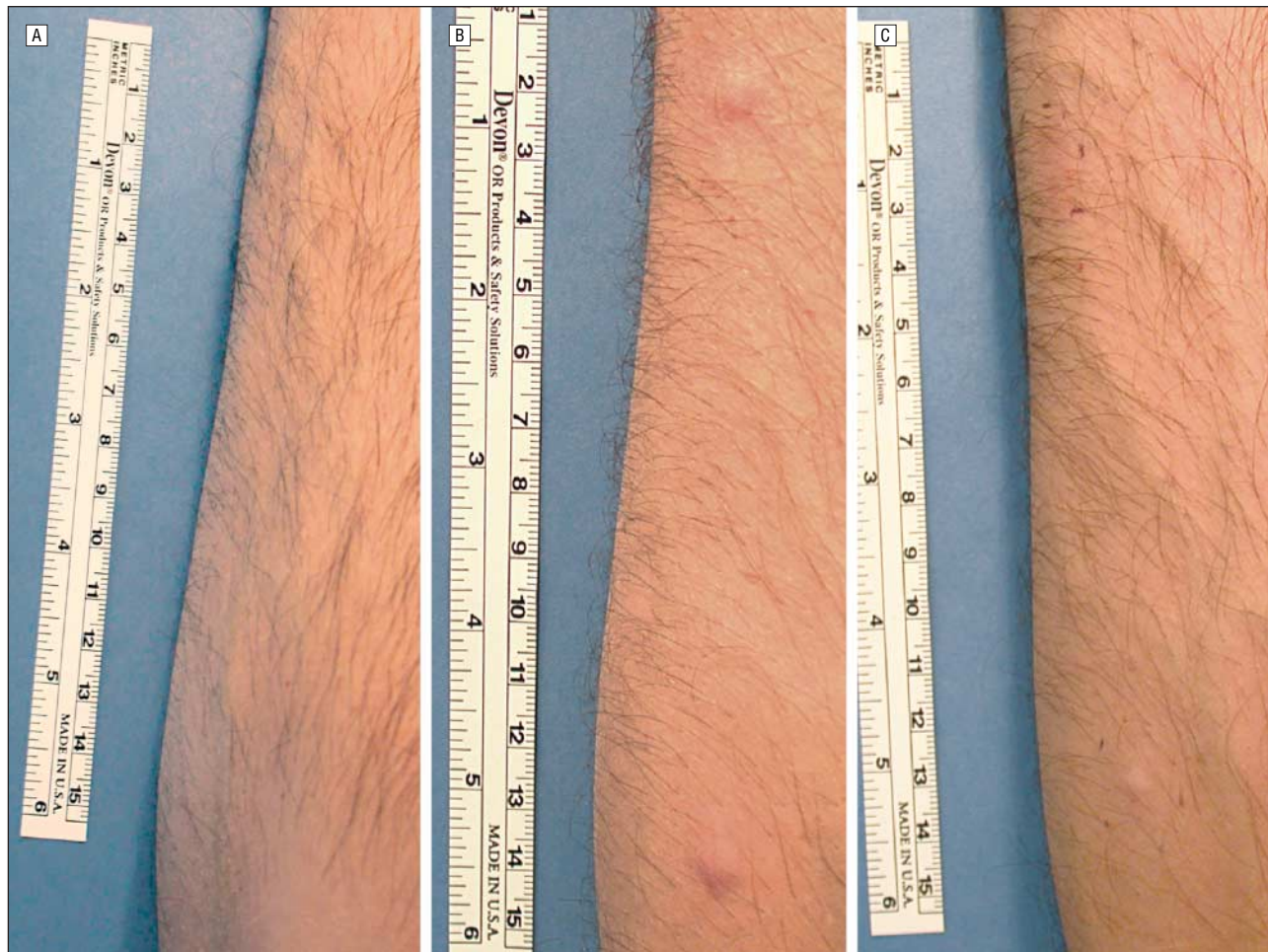


Figure 2. Subject arm before undergoing any injection (A); immediately after injection with nonanimal stabilized hyaluronic acid (NASHA) gel at sites proximal to the wrist (top) and distal to the wrist (bottom) (B); and 1 week after injection of the NASHA gel sites with saline (proximal, top) and hyaluronidase (distal, bottom) (C).

line group, the median skin score was 2. In 92% of the study patients injected with hyaluronidase, there was no tactile trace of injected NASHA gel by 90 days after hyaluronidase injection. In contrast, 100% of the patients injected with saline had a palpable trace of the injected NASHA gel by 90 days after saline injection. The difference in average skin scores between the hyaluronidase and saline groups continued throughout the study and was statistically significant ($P < .001$) in each of the compared time periods (**Table 2**).

No complications were observed in relation to NASHA gel injections during the duration of the study. Subjectively, all 12 patients (100%) reported more burning sensation during the hyaluronidase injection than during the saline injection. Three patients (25%) developed localized allergic reactions to the hyaluronidase injections. In 2 of the allergic patients, localized areas of erythema and pruritis were noted within hours in the location injected with hyaluronidase. No reactions were noted at the saline postinjection sites. The third subject experienced a more intense allergic reaction with an immediate (within 30 minutes) onset of localized erythema accompanied by injection-site pruritus and burning sensation (**Figure 4**). The duration of symptoms was most intense in the initial several hours but lasted for the next 24 hours before declining in intensity. The most se-

verely allergic subject reported (ex post facto) a previous allergy to thimerosal. To eliminate this possible allergen, thimerosal-free hyaluronidase was used in the second part of the study. The same compounding pharmacy prepared the thimerosal-free hyaluronidase. In all 3 cases of allergic reaction, areas of erythema or any residual dyschromia were gone by 4 weeks.

PART 2

Eight volunteers participated in the second part of the study, which involved evaluating the dose-dependent effects of hyaluronidase on post-NASHA palpation scores. Five (63%) of the 8 volunteers were women. The age range of the volunteers was between 30 and 52 years. The mean age of participants was 38.1 years with a median age of 36.5 years. Hyaluronidase doses were randomized to each of the 3 injection sites. In all 3 groups, skin palpation scores declined (**Table 3**). Decreases in average skin scores were most pronounced in the first week after hyaluronidase injection (**Figure 5**). Continual declines in skin scores were noted beyond the first week and well into the third week. Among the 3 groups, average score differences demonstrated a dose-dependent decline in the palpation scores, even though these differences were not statistically significant (Table 3). Comparing the me-

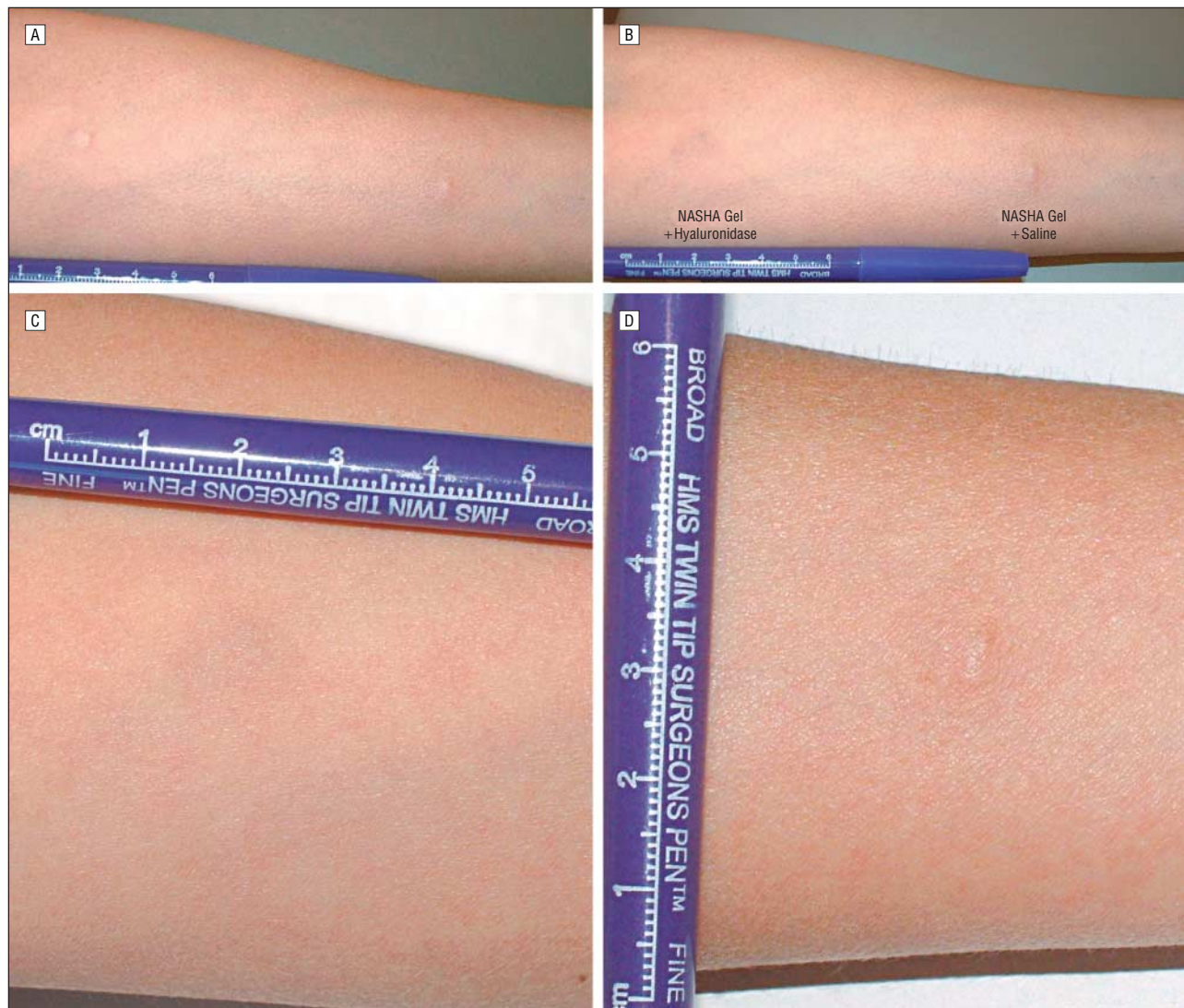


Figure 3. Two days after intradermal injection with 0.2 mL of nonanimal stabilized hyaluronic acid (NASHA) gel proximal (right) and distal (left) to the wrist (A); the NASHA gel-injected sites 4 days after injection with saline (wrist proximal, right) and hyaluronidase (wrist distal, left) (B); close-up images after hyaluronidase (C) and saline (D) injections.

Table 2. NASHA Gel Augmentation Skin Scores After Saline or Hyaluronidase Injections*

Study Group (n = 12)	Baseline	Postinjection Time, d						
		1-3	4-7	8-14	15-28	29-60	61-90	91-120
Saline	3.17 (0.58) 3	3.08 (0.79) 3	2.83 (0.58) 3	2.25 (0.45) 2	2.25 (0.45) 2	2.08 (0.67) 2	2 (0.6) 2	1.67 (0.65) 2
Hyaluronidase	3.08 (0.51) 3	1.5 (0.67) 1	0.67 (0.65) 1	0.42 (0.51) 0	0.17 (0.39) 0	0.17 (0.39) 0	0.08 (0.28) 0	0.08 (0.28) 0
F value	0.14	27.77	74.36	85.87	146.28	73.66	98.63	59.27
P value	.71	<.001	<.001	<.001	<.001	<.001	<.001	<.001

Abbreviation: NASHA, nonanimal stabilized hyaluronic acid.

*Unless otherwise indicated, data are reported as mean (SD) median scores.

dian scores (Tables 3), we found a dose-dependent trend in skin scores. On days 4 to 7 after hyaluronidase injection, the high-dose group median skin score was 0 while the medium- and low-dose groups' median scores were each 1. By the second week, median skin scores in the high- and medium-dose groups declined to 0 while the low-dose group median score was 1.

In response to observed localized allergic reactions in the first part of the study, we used thimerosal-free hyaluronidase to eliminate 1 likely source for the hypersensitivity reactions. Using the thimerosal-free hyaluronidase, we found that 2 (25%) of the 8 subjects developed mild localized allergic responses. No other adverse reactions were noticed. Three of the hyaluronidase-



Figure 4. Localized allergic response 1 day after a 0.5-mL hyaluronidase injection (150 U/mL) into the site of previous augmentation with nonanimal stabilized hyaluronic acid.

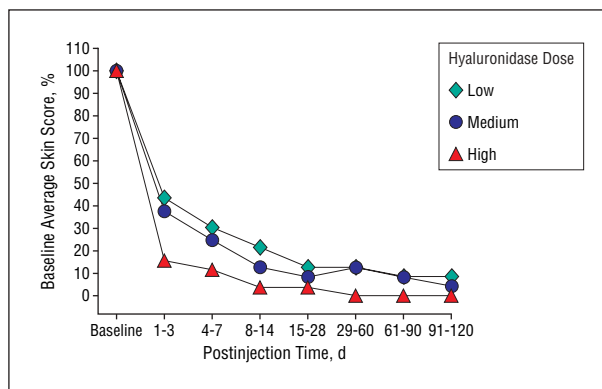


Figure 5. Skin score decline with different doses of thimerosal-free hyaluronidase. Low, medium, and high doses were equivalent to 10, 20, and 30 U of drug, respectively.

Table 3. Skin Scores Before and After Injection With High, Medium, and Low Doses of Hyaluronidase

Dose Group (n = 8)	Postinjection Time, d							
	Baseline	1-3	4-7	8-14	15-28	29-60	61-90	91-120
High (30 U)	3.25 (0.71) 3	0.5 (0.54) 0.5	0.375 (0.52) 0	0.125 (0.35) 0	0.125 (0.35) 0	0 (0) 0	0 (0) 0	0 (0) 0
Medium (20 U)	3 (0.54) 3	1.13 (0.84) 1	0.75 (0.46) 1	0.38 (0.52) 0	0.25 (0.46) 0	0.38 (0.52) 0	0.25 (0.46) 0	0.13 (0.35) 0
Low (10 U)	2.875 (0.35) 3	1.13 (0.64) 1	0.88 (0.84) 1	0.63 (0.52) 1	0.38 (0.52) 0	0.38 (0.52) 0	0.25 (0.46) 0	0.25 (0.46) 0
F value	0.96	2.24	1.38	2.27	0.62	2.10	1.17	1.11
P value	.40	.13	.27	.13	.55	.15	.33	.35

*Unless otherwise indicated, data are reported as mean (SD) median scores.

allergic subjects from the first part of the study were approached for subsequent injections with thimerosal-free hyaluronidase. We wanted to evaluate the contribution of thimerosal to these patients' allergic responses. One subject refused while the other 2 subjects accepted additional injections with thimerosal-free hyaluronidase. Both allergic patients from the first part of the study experienced similar, albeit milder, self-limiting localized reactions. In 1 patient, there was a clear visual suggestion that allergic response to injected hyaluronidase was dose dependent (**Figure 6**).

COMMENT

Hyaluronidase, better known to most physicians by its previous trade name, Wydase (Wyeth Laboratories, Philadelphia, Pa), was discontinued by the manufacturer in early 2001.⁸ Its discontinuation was ascribed to economic and manufacturing quality-assurance issues and not to a change in the drug's efficacy or a decline in its safety profile.^{8,9} With the disappearance of Wydase, our supply of hyaluronidase for cutaneous surgery and this study was obtained from a reliable compounding pharmacy. Currently, 2 new hyaluronidase formulations, Amphadase (Amphastar Pharmaceuticals; Rancho Cucamonga, Calif) and Vitrase (ISTA Pharmaceuticals; Irvine, Calif) have gained FDA approval.^{10,11} Neither product was available at the commencement of the present study.

The use of hyaluronidase for reduction of NASHA gel skin augmentation is an off-label application of its FDA-approved indications. Patients should be made aware of this fact in the informed consent process. As a category C drug, hyaluronidase use in pregnant or expectant women has not been adequately studied and should be avoided.

With the expanded use of Restylane and other NASHA gel products, a compound that could reduce NASHA gel-induced dermal augmentation would be useful. Based on this study, hyaluronidase provides promise as such an agent. The availability of a reversing agent for NASHA gel is a unique correction mechanism that is not available for dermal fillers that do not contain hyaluronic acid. For 6 months prior to initiation of the study, we had used hyaluronidase in several patients to correct areas of NASHA gel overinjection and had good results. To scientifically evaluate these isolated experiences, we undertook this study. To minimize sources of errors, we used a number of safeguards. Injection sites were randomized, and a single, independent, noninjecting evaluator was blinded to the postinjection material. In each patient, postinjection locations were randomized to minimize the contributions of differing forearm skin thickness. Each patient served as his or her own control. The results demonstrated a statistically significant amelioration of NASHA gel augmentation by hyaluronidase. The dose dependency of this effect was apparent numerically and graphically, even though it failed to be statistically significant.

In the first part of the study, we were surprised at the 3 cases of localized hypersensitivity to injected hyal-

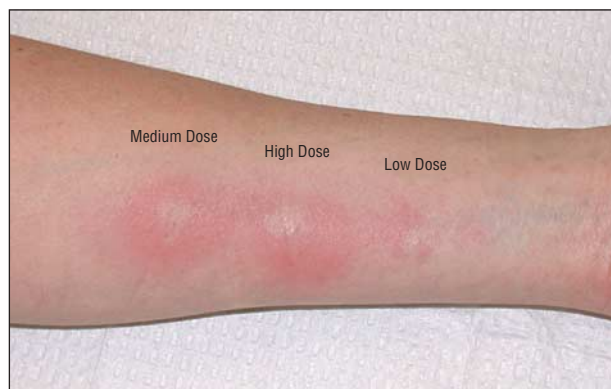


Figure 6. Reactions to different doses of thimerosal-free hyaluronidase. Low, medium, and high doses were equivalent to 10, 20, and 30 U of drug, respectively.

uronidase. This unexpected finding prompted us to look for etiologic sources in our hyaluronidase. The first suspected agent was thimerosal, which is a mercury-containing preservative used in some pharmacologic agents. Our initial thinking was prompted by the fact that the most severely allergic subject had a documented allergy to thimerosal-containing contact lens solutions. In response, we ordered thimerosal-free hyaluronidase from our compounding pharmacy. However, even with the thimerosal-free hyaluronidase, an unexpectedly high percentage of patients (25%; $n=3$) had hyaluronidase injection site redness and mild pruritus.

In our surgical practice of using hyaluronidase as an additive to local anesthetic solution, we never noticed any allergic reactions, and this unscientific observation was corroborated by the experience of other physicians we have consulted. One consideration is the relatively low dose of hyaluronidase actually delivered when the drug is added to local anesthetic solution. The typical 1:10 to 1:50 dilution range used in local anesthetic is equivalent to 15 to 3 U of hyaluronidase per milliliter of local anesthetic solution. For comparison, in part 1 of this study, the total hyaluronidase dose administered per patient was 75 U. The total dose injected per patient in part 2 of the study was equal to 60 U (high dose [30 U] + medium dose [20 U] + low dose [10 U]). Furthermore, in contrast to the diffuse infiltration of hyaluronidase mixed with local anesthetic, the injections in this study were concentrated in localized deposits in areas already stimulated by the previous injection of NASHA gel. These factors may have made the hyaluronidase injections more immunogenic.

Allergic reactions to hyaluronidase are not commonly seen in patients but have been documented in a number of reports.¹²⁻²⁰ Individuals with bee- or vespid-sting allergies are at higher theoretical risk for hyaluronidase hypersensitivity owing to the presence of hyaluronidase in the venom.^{21,22} In 1 clinical case report, a type I allergic reaction to hyaluronidase occurred when concentrated drug (7500 U/mL) was injected during ophthalmic surgery.¹² Another report describes allergic reactions involving 3 cases of angioedema relating to hyaluronidase use during cataract surgery. All 3 patients in that report subsequently skin tested positively

for hyaluronidase.¹³ Skin testing was positive for hyaluronidase in another case report involving hyaluronidase allergies.¹⁴ In all of these cases, significantly higher doses of hyaluronidase were delivered than is typically used for cutaneous surgical infiltration. In contrast, in a study by Nevarre and Tzarnas,⁷ 25 volunteers received a 0.5-mL intradermal injections of 1% lidocaine with 7.5 U of hyaluronidase, and no allergic events were noted. This study tends to reinforce the notion that lower doses of hyaluronidase may be less likely to precipitate an allergic response. Outside of the present study, we have observed no allergic reactions with low-dose hyaluronidase injections used for reducing NASHA gel augmentation.

All studies have limitations that should be discussed. While tremendous efforts were taken to standardize the scoring scales, the use of finger palpation may have masked subtle differences in palpation scores. Use of a larger study group might have further contributed to the validity of our observations. Both of these factors might have had the greatest impact on determining the dose-response relationships examined in the second part of the study. In retrospect, we should have added a third NASHA gel injection site without a postinjection of any kind to more clearly compare the effects on skin scores of hyaluronidase vs no postinjections. Our initial evaluation process also included close-up photographic images of the injection sites. Significant limitations in estimating and analyzing the size of the injected areas led us to abandon photoanalysis as an outcomes measurement tool in this study.

Fortunately, NASHA gel-induced cutaneous deformities are not common, but they can be disconcerting when they occur and persist beyond an initial period. The best defenses against such cutaneous deformities are proper selection of facial lines, use of precise injection technique, and avoidance of overcorrection. Generally, we find that patients tolerate "lumps and bumps" for up to a week before becoming concerned. After a 2-week waiting period, hyaluronidase injections may be useful in decreasing the volume of injected NASHA gel. In cases where small areas of overinjection need to be "fine tuned," the injection of higher doses of hyaluronidase may break down more NASHA gel than intended. Hence, a small dose of hyaluronidase, equivalent to 5 to 10 U (0.1-0.2 mL of drug at 50 U/mL) may be injected. The use of a smaller initial dose might also eliminate the chance for an allergic response. Repeated injections can be offered in 2-week intervals if indicated. If larger doses are to be used, we recommend performing skin testing prior to injecting facial areas.

In conclusion, hyaluronidase can be used to hasten the diminution of augmentation produced by previously injected intradermal Restylane (NASHA gel). An initial injection dose between 5 and 10 U of hyaluronidase can be used and repeated as needed.

Accepted for Publication: May 17, 2004.

Correspondence: A. John Vartanian, MD, 520 E Broadway Ave, Suite 200, Glendale, CA 91205 (drvartanian@yahoo.com).

REFERENCES

1. Friedman PM, Mafong EA, Kauvar ANB, Geronemus RG. Safety data of injectable nonanimal stabilized hyaluronic acid gel for soft tissue augmentation. *Dermatol Surg*. 2002;28:491-494.
2. Narins RS, Brandt R, Leyden J, Lorenc ZP, Rubbin MG, Smith S. A randomized, double-blind, multicenter comparison of the efficacy and tolerability of Restylane versus Zyplast for the correction of nasolabial folds. *Dermatol Surg*. 2003;29:588-595.
3. Carruthers J, Carruthers A. A prospective, randomized, parallel group study analyzing the effect of BTX-A (Botox) and nonanimal sourced hyaluronic acid (NASHA, Restylane) in combination compared with NASHA (Restylane) alone in severe glabellar rhytides in adult female subjects: treatment of severe glabellar rhytides with a hyaluronic acid derivative compared with the derivative and BTX-A. *Dermatol Surg*. 2003;29:802-809.
4. Andre P. Evaluation of the safety of a non-animal stabilized hyaluronic acid (NASHA—Q-Medical, Sweden) in European countries: a retrospective study from 1997 to 2001. *J Eur Acad Dermatol Venereol*. 2004;18:422-425.
5. Merck & Co Inc. *The Merck Index*. 13th ed. White Station, NJ: Merck & Co Inc; 2001:4777.
6. Clark LE, Mellette JR Jr. The use of hyaluronidase as an adjunct to surgical procedures. *J Dermatol Surg Oncol*. 1994;20:842-844.
7. Nevarre DR, Tzarnas CD. The effects of hyaluronidase on the efficacy and on the pain administration of 1% lidocaine. *Plast Reconstr Surg*. 1998;101:365-369.
8. Merchant B; Merchant-Taylor International Inc [letter]. Available at: <http://www.fda.gov/ohrms/dockets/dailys/03/jul03/072503/02p-0506-c000001-vol1.pdf>. Accessed May 11, 2005.
9. Department of Health and Human Services. Federal Register Notice. Available at: <http://www.fda.gov/ohrms/dockets/98fr/03-072880.pdf>. Accessed May 11, 2005.
10. US Food and Drug Administration. A catalog of FDA approved drug products. Available at: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=AMPHADASE>. Accessed May 11, 2005.
11. US Food and Drug Administration. A catalog of FDA approved drug products. Available at: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=VITRASE>. Accessed May 11, 2005.
12. Kirby B, Butt A, Morrison AM, Beck MH. Type I allergic reaction to hyaluronidase during ophthalmic surgery. *Contact Dermatitis*. 2001;44:52.
13. Eberhart AH, Weiler CR, Erie JC. Angioedema related to the use of hyaluronidase in cataract surgery. *Am J Ophthalmol*. 2004;138:142-143.
14. Minning CA Jr. Hyaluronidase allergy simulating expulsive choroidal hemorrhage. *Arch Ophthalmol*. 1994;112:585-586.
15. Taylor IS, Pollowitz JA. A little-known phenomenon: allergic reaction to hyaluronidase. *Ophthalmology*. 1984;91:1003.
16. Kind LS, Roffler S. Allergic reactions to hyaluronidase. *Proc Soc Exp Biol Med*. 1961;106:734-735.
17. Kempeneers R, Draland L, Ceuppens J. Hyaluronidase induced orbital pseudo-motor as a complication of retrobulbar anaesthesia. *Bull Belgian Soc Ophthalmol*. 1992;243:159-166.
18. Ahluwalia HS, Lukaris A, Lane CM. Delayed allergic reaction to hyaluronidase: a rare sequel to cataract surgery. *Eye*. 2003;17:263-266.
19. Quhill F, Bowling B, Packard RB. Hyaluronidase allergy after peribulbar anesthesia with orbital inflammation. *J Cataract Refract Surg*. 2004;30:916-917.
20. Szeplalusi Z, Nentwich I, Dobner M, Pilwein K, Urbanek R. IgE-mediated allergic reaction to hyaluronidase in paediatric oncological patients. *Eur J Pediatr*. 1997;156:199-203.
21. King TP, Spangfort MD. Structure and biology of stinging insect venom allergens. *Int Arch Allergy Immunol*. 2000;123:99-106.
22. Franklin R, Baer H. Comparison of honeybee venoms and their components from various sources. *J Allergy Clin Immunol*. 1975;55:285-298.

Correction

Errors in Abstract and Text. In the "Results" sections of the abstract and text of the article "Color-Specific Enhancement of Digital Photographs for Identification of the Extent of Cutaneous Malignancy" by Krein et al, published in the March/April issue of the ARCHIVES (2005; 7:135-137), the statement "... with fair accuracy in 2 cases" should have read "... with fair accuracy in 3 cases."