

Hyaluronidase in the correction of hyaluronic acid-based fillers: a review and a recommendation for use

Berthold Rzany, MD, ScM,¹ Petra Becker-Wegerich, MD,² Frank Bachmann, MD,¹ Ricardo Erdmann,¹ & Uwe Wollina, MD³

¹Division of Evidence-based Medicine, Klinik für Dermatologie, Charité Universitätsmedizin, Berlin, Deutschland

²Ästhetik- und Laserzentrum, Meilen, Schweiz

³Klinik für Dermatologie und Allergologie am Krankenhaus Dresden-Friedrichstadt, Dresden, Deutschland

Summary

Background Hyaluronic acid (HA) preparations are the most commonly used injectable fillers in esthetic medicine. In contrast to other injectable fillers with hyaluronidase, there is a tool available to reduce unwanted depots of this filler.

Aims The aim of this paper is to give an overview on the present literature and in addition to give some recommendations for use based on the experience of the authors.

Methods The overview is based on a literature search.

Results There is some evidence from two smaller clinical trials that hyaluronidase will effectively decrease injected depots of HA. It has further been shown from case series and case reports that this reduction is clinically relevant. There is less evidence that hyaluronidase is also helpful in adverse reactions to HA-based fillers.

Conclusions The reports suggest that the treatment is safe. However, adverse reactions to hyaluronidase such as allergic reactions have been reported. Patient should be informed about that before treatment.

Keywords: hyaluronidase, hyaluronic acid

Introduction

Hyaluronic acid (HA)-based fillers are the most commonly used fillers.^{1,2} With the increased involvement of sometimes inexperienced colleagues and nonphysicians like nurses and nonmedical practitioners as beauticians and natural healers ('Heilpraktiker') the risk of unwanted results rises. Unwanted results can mean overcorrection and asymmetries as well as adverse events to these injectable fillers. Although hyaluronic-based fillers are defined as temporary materials, they can last up to 12 months or longer.³

Hyaluronidase destroys HA and gives the possibility to adjust overcorrection and asymmetries. Furthermore, hyaluronidase has also been suggested for the treatment of the rare adverse reactions to HA fillers as by hypothesis some of the HA might still be present in the skin which might be targeted by hyaluronidase.

The aim of this review is to present the evidence for the efficacy and safety of hyaluronidase and to discuss proposals of use for this indication.

Methodology

Literature was searched through MEDLINE for case reports or case series on hyaluronidase in the treatment of unwanted HA depots or adverse reactions to HA. The search comprised all literature until August 2008. The literature was analyzed separately for papers focusing on the treatment of overcorrections and adverse reactions toward HA.

Correspondence: Prof. Dr. med. B Rzany, Department of Dermatology, Division of Evidence Based Medicine, Charité Universitätsmedizin Berlin, Charitéplatz 1, D-10117 Berlin, Germany. E-mail: berthold.rzany@charite.de

Accepted for publication July 21, 2009

Table 1 Summary of experimental studies in humans demonstrating the efficacy of hyaluronic acid in reducing the depots of injected hyaluronidase

References	No. of patients/ gender/age	Setting	Study drug	Follow-up	Adverse events to hyaluronidase
Vartanian <i>et al.</i> ⁴ (Part 1)	12 subjects/7 female (58%), 5 male (42%)/ Mean age: 43.7 years	Double-blinded, randomized clinical trial Experimental design Two ipsilateral forearm injections of NASHA gel each	0.5 mL of 0.9% saline or 0.5 mL of hyaluronidase (150 U/mL, equivalent to 75 U of hyaluronidase)	Dramatic decline in palpation scores occurred between days 4 and 7 after hyaluronidase injection	All 12 patients (100%) reported more burning sensation during the hyaluronidase injection than during the saline injection Three patients (25%) developed localized allergic reactions (erythema, pruritus) to the hyaluronidase injections
Vartanian <i>et al.</i> ⁴ (Part 2)	8 volunteers/5 female (63%)/Mean age: 38.1 years	Randomized blinded evaluator Randomly selected NASHA gel injection sites (0.2 mL) Received an equal volume (0.4 mL) of one of three different concentrations of 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) Thimerosal-free hyaluronidase	In all three groups, skin palpation scores declined A dose-dependent decline in the palpation scores could be found, even though these differences were not statistically significant	Two (25%) of the eight subjects developed mild localized allergic responses No other adverse reactions were noticed

Results

We were able to find several papers focusing on hyaluronidase as a corrective tool for HA in esthetic medicine.

Two experimental studies focused on the principals of efficacy of hyaluronidase in reducing depots of HA.

Experimental studies in humans

These two small prospective randomized studies ($n = 12$ and $n = 8$) were conducted sequentially by Vartanian *et al.*⁴ to determine the efficacy and dose dependency of hyaluronidase on NASHA gel implants (Table 1). The first arm of the study was intended to compare the effects of injected hyaluronidase or saline on sites of previous NASHA gel injections. The second arm was designed to evaluate the dose-dependent effects of injected hyaluronidase on NASHA gel augmentation sites.

These are quite small experimental studies and, in fact, there was only a trend of a dose–response relationship. However, they demonstrate the efficacy of hyaluronidase in reducing small amounts of injected HA.

Efficacy of hyaluronidase in reducing unwanted depots of hyaluronic acid

Most papers focus on the effect of hyaluronidase in reducing unwanted depots of HA (Table 2).

In addition to these case reports, one large case series can be found. The purpose of the case series comprising 155 patients was to describe the authors' experience with the treatment of periorbital hollows with HA (Restylane, Q-Med, Uppsala, Sweden).⁵ For some reason, 11% of patients ($n = 17$) received hyaluronidase to reduce contour irregularities. The typical dose used was 0.3–1.0 mL of a 15 U/mL solution. The authors report incomplete response to the attempts to decrease the residual HA gel by using hyaluronidase injections when the unwanted effect was a doughy edema.

In addition, two papers could be found that focused on the reduction of HA depots in patients with probable vascular reactions (Table 3).

Hyaluronidase to reduce the effects of adverse reactions to hyaluronic acid preparations

Three papers could be found focusing on the effect of hyaluronidase on the treatment of adverse reactions to HA (Table 4).

Safety of hyaluronidase

Adverse reactions to hyaluronidase are rare. In his case series, e.g., Sopokar *et al.*⁶ reported only in 2 of 97 treated patients a temporary postinjection pruritus. However, allergic and even a few anaphylactic reactions have been associated with hyaluronidase. Most reports

Table 2 Case reports on hyaluronidase reducing unwanted depots of hyaluronic acid preparations

References	No. of patients, gender, age	Diagnosis	Hyaluronidase used	Follow-up	Adverse events to hyaluronidase
Lambros ¹⁷	1 female patient, 35 years old	Lumpiness after HA injections	75 Units of hyaluronidase (Lee Pharmacy, Inc.; 50 U/cc) and 1.5 cc of 0.5% lidocaine with epinephrine	Successful dissolution: 90% in 24 h	None
Soparkar <i>et al.</i> ²¹	1 female patient, 65 years old	Persistent sausage whisker-like reaction immediately after Restylane injection 63 months ago	100 U/mL, using 0.025–0.05 mL at each side (local pharmacist)	One week later => complete resolution of the "sausage whiskers"	None
Hirsch <i>et al.</i> ¹⁸	1 female patient, 44 years old	Bluish discoloration after Juvéderm™ (Allergan, Inc., Irvine, CA, USA) injection from a nonexperienced injector	75 Units of hyaluronidase enzyme (Vitrace™, IstaPharmaceuticals) Further 75 units several days later	First improvement within 4 days, complete clearance	None mentioned
Hirsch and Cohen ¹⁹	1 female, patient, 56 years old	Blue-gray infraorbital nodule 2 weeks post-Restylane injection in the nasojugal folds	75 Units of amphotase was immediately injected into and around the infraorbital nodule	Within 72 h almost complete resolution of the lump	None
Andre and Levy ²²	1 female, patient 25 years old	HA injection 1 month ago; soft, lumpy, bluish mass; overcorrection (blue mass) periocular after HA injection (Surgiderm 30XP)	4% Ovine-derived hyaluronidase (Desinfital; Aesthetic Dermal, Girona, Spain) (1 vial 1500 IU. diluted with 4 mL) Injection of 0.3mL = 150 U	Within 10 min already some effects, after 1 h approximately 50% of the mass had already disappeared, after 12 h complete disappearance	No pain during treatment No adverse events
Brody ²³ (see also below)	(1) 64-year-old patient (2) 45-year-old female	(1) Pearly, contiguous, slightly blue, soft mass under each eye (2) Left side of her nasolabial fold was larger than her right and she thought that the material "moved over into the fold"	(1) 1 cc of 75 units of hyaluronidase (150 units/cc) combined with 1.5 cc of 1% lidocaine with epinephrine (2) 0.5 cc of a solution of 75 units of hyaluronidase mixed with 1% lidocaine with epinephrine	(1) Disappearance of most of the material within 24 h; reinjection or remaining nodules with 0.1 cc of hyaluronidase Solution with dissolution of the remaining material within 5 days (2) Little improvement => her left side has always been slightly larger than that on her right side	(1) Mild erythema; mild ecchymosis (2) Slight erythema within 24 h

are based on ophthalmological or other nonesthetic interventions.^{7–10} In addition, a couple of reports after the use of ovine as well as bovine hyaluronidase for esthetic indications can be found¹¹ (Becker-Wegerich 2009, personal communication). In both cases, edema developed rapidly after the injection. The edema was controlled by steroid injections.

Available hyaluronidase preparations in Europe (Table 5)

Most available hyaluronidase products use hyaluronidase of bovine origin. In addition, hyaluronidase of ovine origin exists.

Hylase® "Dessau"

Hyaluronidase (Hylase® "Dessau", Riemser Arzneimittel AG, Greifswald - Insel Riems, Germany) was developed as a spreading or diffusing substance to increase the permeability of connective tissue through the hydrolysis of HA. The enzyme is extracted from bovine testes. The bovine testes used are obtained from New Zealand from a source which is recognized as being completely BSE (Bovine Spongiform Encephalopathy) free.

Hyaluronidase is an enzyme that breaks down HA (hyaluronan) by cleaving glycosidic bonds of HA and, to some extent, other acid mucopolysaccharides of the

Table 3 Case reports focusing on the effects of hyaluronidase in impending vascular reactions

References	No. of patients/ gender/age	Diagnosis	Hyaluronidase used	Follow-up	Adverse events to hyaluronidase
Hirsch <i>et al.</i> 2007 ²⁴	1 female patient/ 44 years old	Probable vascular reaction with impending necrosis after treatment of the nasolabial fold	30 Units of hyaluronidase (exact product information not given) In addition pretreatment aspirin p.o. and topical nitroglycerin paste as well as hot compresses	Eight hours later the lip and area previously observed to be under vascular compromise was pinkish; 2 weeks later there was no evidence of any residual adverse event	None
Hirsch <i>et al.</i> ²⁵	1 female patient/ 43 years old	>48 h after injection of the nasolabial fold patchy cutaneous erythema and violaceous foci	30 Units of hyaluronidase	Day 3 after hyaluronidase injection: continuing improvement in pain, color and physical appearance	None

Table 4 Effect of hyaluronidase on the improvement of adverse reactions to hyaluronic acid preparations

References	No. of patients/ gender/age	Diagnosis	Hyaluronidase used	Follow-up	Adverse events to hyaluronidase
Soparkar and Patrinely ²⁶	62-year-old woman	Severe dermal inflammatory reaction to Restylane	A total of five injections accounting for 375 units of hyaluronidase over a period of 2 weeks Patient received in addition oral Levofloxacin and oral steroids	Good results after 4 months	None
Brody ²³ (see above)	68-year-old female	Within 1 week after injection => redness, bumpiness, tenderness, and warmth; multiple warm, red, indurated nodules after nonanimal-stabilized hyaluronic acid; additional bovine collagen	15 Units (0.2 cc of a solution of 75 units) of hyaluronidase combined with 1% lidocaine with epinephrine as well as topical steroids and oral antibiotics and weekly courses of prednisone	Within 24 h, the patient noted the disappearance of the nodule without recurrence	None
Becker-Wegerich ²⁷	1 female patient/ 49 years old	Approximately 1 cm large and bluish nodules 8 months after the injection of Restylane Vital in the dorsum of the hand	Hyaluronidase (Hylase Dessau) two injections with 0.2 mL per node, 3 days from each apart (150 units were diluted with 1 mL saline)	Flattening of the nodules	None

Table 5 Available hyaluronidase preparations in Europe

Name	Company	Units per vial	Origin	References
Hylase Dessau	Riemser Arzneimittel AG, Germany	150*, 300, 1500	Bovine	12
Desinfital	Aesthetic Dermal, UK	1500	Ovine	22

*Usually the 150-U vial is sufficient when used to remove unwanted depots of hyaluronic acid.

connective tissue.¹² The physiologic role of hyaluronidase is seen in stimulating angiogenesis by defragmenting HA. The fibrotic healing of adult and late gestational wounds correlates with an increased hyaluronidase activity and a removal of hyaluronan.¹³ Further consideration see hyaluronidase as a regulatory agent in HA homeostasis and metabolism.¹⁴ Hyaluronidase cannot cross the blood–brain barrier.¹⁵ The clinical use and therapeutic benefits of hyaluronidase began in the early 1950s. In 1952, Breu discovered that the enzyme is capable of spreading dyes or other substances in tissue and of significantly increasing the permeability of skin and connective tissue via the breakdown of HA. The enzyme hyaluronidase is a “hydrolase” with a molecular weight of approximately 60 000 Da.¹⁶

Hylase[®] “Dessau” comes as a white powder which needs to be diluted with saline before injection. The smallest vial available contains 150 U. The product contains no preservatives. The product is manufactured during a sophisticated multistep procedure established and patented in Germany for many decades. It is a highly purified bovine protein extract with a low allergic or sensitizing potential.

Hylase[®] “Dessau” must be stored at cool temperatures (2–8 °C). These conditions guarantee the constant quality of the product over a long period. Additional tests have shown the stability of the product at controlled room temperature (25 °C ± 2 °C/60% relative humidity [RH] ± 5% RH) over a period of at most 12 months (Supplementary Protection Certificate).

Other hyaluronidase preparations

In the literature, several other hyaluronidase preparations were used. In the earlier papers, hyaluronidase derived from Lee Pharmacy, Inc., Fort Smith, AZ, USA; 50 U/cc.¹⁷ Hirsch *et al.*^{18,19} used Vitrase[™], IstaPharmaceuticals (http://www.istavision.com/products/products_vitraser200.asp). Vitrase is a preparation of purified ovine (sheep) testicular hyaluronidase, a protein enzyme. It contains an active component: 200 USP units/mL of ovine hyaluronidase. Amphadase (Amphastar Pharmaceuticals, Inc., Rancho Cucamonga, CA, USA), another hyaluronidase product, is also a preparation of a bovine source. Each vial contains 150 USP units of hyaluronidase per mL.

Hylenex[®] recombinant (Baxter Healthcare Corporation and Halozyme Therapeutics, Inc.) is a purified preparation of recombinant hyaluronidase from Chinese Hamster Ovary cells. The purified glycoprotein contains 447 amino acids and has a molecular weight of approximately 61 000 Da. Each milliliter of this

preparation contains 150 USP units of recombinant human hyaluronidase per milliliter.²⁰

Practical consideration

Although there are no large randomized-controlled trials on the efficacy of hyaluronidase in reducing unwanted depots of HA, based on the reviewed literature and based on the personal experience of the authors some practical considerations can be given.

In the case of unwanted depots of HA, the following steps should be performed:

- Inform the patient that hyaluronidase is not licensed so far for the treatment of unwanted HA depots.
- Inform also the patient that in rare cases, adverse reactions to the hyaluronidase have been known. Do NOT skin test. The allergic reactions are quite rare and cannot totally be excluded by skin test.
- Do NOT treat patients with a known allergy to bovine protein if the hyaluronidase used derives from bovine material.
- Dilute the hyaluronidase (150 U vial) with 0.9% saline (1 mL) and inject the mixture in the HA depots. There is NO evidence that the addition of lidocaine or epinephrine is helpful. The volume used depends on the quantity of injected HA. Usually 0.05–0.1 mL per injection point (7.5–15 U) is sufficient. Inject slowly.
- Choose the needle size according to the location and the size of the depot. Use a 30-gauge (0.3 × 13 mm) needle for more superficial nodules and a 27-gauge (0.4 × 20 mm) or a 26-gauge (0.45 × 10mm) needle for deeper nodules.
- Make sure to inject in the HA depot; in cases of very superficial HA depots, inject just beneath the depot.
- For nodules exclusively due to HA, some patients notice an obvious decrease or a disappearance of the nodule within 24–48 h. For nodules of unknown cause, an obvious reduction of inflammation and size has been induced in some patients. Usually, an apparent regression is noticeable within 24–48 h; however, in inflamed nodules a complete disappearance may take longer. Therefore, a control visit should be scheduled about 2 weeks after the injection.
- If the nodule is very inflamed and an abscess may be likely an adjuvant systemic antibiotic treatment, e.g., with ciprofloxacin or levofloxacin 250 mg once daily, should be initiated as hyaluronidase may act as the spreading factor.
- For the same reason (potentially increased spreading) hyaluronidase should not be injected in an area that has been treated with botulinum toxin A in the last 48 h.

- If an immediate reaction occurs treat accordingly to the prevailing symptoms. As for every allergic reaction, an allergy pass card should be issued. Furthermore, an allergological workup is recommended.

Conclusions

HA preparations are the most used injectable fillers on the market. As the esthetic market is growing, more and more patients will be treated with HA. This will lead to more patients with a relative or absolute overcorrection and patients who suffer from immediate or long-term adverse events from these products. A product like hyaluronidase can therefore be considered as a rescue-medication which can help reverse overcorrection or some more severe complications.

There is some evidence from two smaller clinical trials that hyaluronidase will effectively decrease injected depots of HA. There is further evidence from case series and case reports that this reduction is clinically relevant. There is very little evidence that hyaluronidase is also helpful in adverse reactions to HA-based fillers.

The reports suggest that the treatment is safe. However, adverse reactions, as allergic reactions, to hyaluronidase of bovine or ovine origin have been reported. Patients should be informed about that before treatment.

Colleagues should be instructed about this very beneficial tool and how it should be used.

References

- 1 De Maio M, Rzany B. *Injectable Fillers in Aesthetic Medicine*. Heidelberg: Springer; 2006; ISBN 3-540-23941-3.
- 2 Monheit GD, Coleman KM. Hyaluronic acid fillers. *Dermatol Ther* 2006; **19**(3): 141–50.
- 3 Narins RS, Dayan SH, Brandt FS, Baldwin EK. Persistence and improvement of nasolabial fold correction with nonanimal-stabilized hyaluronic acid 100,000 gel particles/mL filler on two retreatment schedules: results up to 18 months on two retreatment schedules. *Dermatol Surg* 2008; **34**(Suppl. 1): S2–8.
- 4 Vartanian AJ, Frankel AS, Rubin MG. Injected hyaluronidase reduces restylane-mediated cutaneous augmentation. *Arch Facial Plast Surg* 2005; **7**(4): 231–7.
- 5 Goldberg RA, Fiaschetti D. Filling the periorbital hollows with hyaluronic acid gel: initial experience with 244 injections. *Ophthalm Plast Reconstr Surg* 2006; **22**(5): 335–41.
- 6 Soparkar CN, Patrinely JR, Skibell BC, Tower RN. Hyaluronidase and Restylane. *Arch Facial Plast Surg* 2007; **9**(4): 299–300.
- 7 Agrawal A, McLure HA, Dabbs TR. Allergic reaction to hyaluronidase after a peribulbar injection. *Anaesthesia* 2003; **58**(5): 493–4.
- 8 Ahluwalia HS, Lukaris A, Lane CM. Delayed allergic reaction to hyaluronidase: a rare sequel to cataract surgery. *Eye* 2003; **17**(2): 263–6.
- 9 Leibovitch I, Tamblin D, Casson R, Selva D. Allergic reaction to hyaluronidase: a rare cause of orbital inflammation after cataract surgery. *Graefes Arch Clin Exp Ophthalmol* 2006; **244**(8): 944–9.
- 10 Müller U, Bircher A, Bischof M. Allergisches Angioödem nach zahnärztlicher Applikation eines Lokalanästhetikum und Hyaluronidase enthaltenden Vorspritzmittels. *Schweiz Med Wochenschr* 1986; **116**: 1810–1813.
- 11 Andre P, Flechet ML. Angioedema after ovine hyaluronidase injection for treating hyaluronic acid overcorrection. *J Cosmet Dermatol* 2008; **7**(2): 136–8.
- 12 European Pharmacopoeia 6.0: European Directorate for the Quality of Medicines; 2008; 978-92-871-6328-8 (online). <http://www.digento.de/titel/103336.html>.
- 13 West DC, Shaw DM, Lorenz P, Adzick NS, Longaker MT. Fibrotic healing of adult and late gestation fetal wounds correlates with increased hyaluronidase activity and removal of hyaluronan. *Int J Biochem Cell Biol* 1997; **29**(1): 201–10.
- 14 Schwartz DM, Jumper MD, Lui GM, Dang S, Schuster S, Stern R. Corneal endothelial hyaluronidase: a role in anterior chamber hyaluronic acid catabolism. *Cornea* 1997; **16**(2): 188–91.
- 15 Jiang D, Liang J, Noble PW. Hyaluronan in tissue injury and repair. *Annu Rev Cell Dev Biol* 2007; **23**: 435–61.
- 16 Breu W. Hyaluronidase. *Wien Med Wochenschr* 1952; **102**(23): 435–7.
- 17 Lambros V. The use of hyaluronidase to reverse the effects of hyaluronic acid filler. *Plast Reconstr Surg* 2004; **114**(1): 277.
- 18 Hirsch RJ, Narurkar V, Carruthers J. Management of injected hyaluronic acid-induced Tyndall effects. *Lasers Surg Med* 2006; **38**(3): 202–4.
- 19 Hirsch RJ, Cohen JL. Challenge: Correcting superficially placed hyaluronic acid. *Skin Aging* 2007; **15**: 36–8.
- 20 Yocum RC, Kennard D, Heiner LS. Assessment and implication of the allergic sensitivity to a single dose of recombinant human hyaluronidase injection: a double-blind, placebo-controlled clinical trial. *J Infus Nurs* 2007; **30**(5): 293–9.
- 21 Soparkar CN, Patrinely JR, Tschen J. Erasing restylane. *Ophthalm Plast Reconstr Surg* 2004; **20**(4): 317–8.
- 22 Andre P, Levy PM. Hyaluronidase offers an efficacious treatment for inaeesthetic hyaluronic acid overcorrection. *J Cosmet Dermatol* 2007; **6**(3): 159–62.
- 23 Brody HJ. Use of hyaluronidase in the treatment of granulomatous hyaluronic acid reactions or unwanted hyaluronic acid misplacement. *Dermatol Surg* 2005; **1**: 893–7.
- 24 Hirsch RJ, Cohen JL, Carruthers JD. Successful management of an unusual presentation of impending necrosis following a hyaluronic acid injection embolus and a proposed algorithm for management with hyaluronidase. *Dermatol Surg* 2007; **33**(3): 357–60.

- 25 Hirsch RJ, Lupo M, Cohen JL, Duffy D. Delayed presentation of impending necrosis following soft tissue augmentation with hyaluronic acid and successful management with hyaluronidase. *J Drugs Dermatol* 2007; **6**(3): 325–8.
- 26 Soparkar CN, Patrinely JR. Managing inflammatory reaction to restylane. *Ophthal Plast Reconstr Surg* 2005; **21**(2): 151–3.
- 27 Becker-Wegerich P. New indications for Hyaluronic acid of the NASHA-gel-generation—highlights from aesthetical dermatology in clinical daily routine. *J Dtsch Dermatol Ges* 2008; **6**(Suppl. 3): S3–20.