

# HYALURONIDASE

TO TREAT HYALURONIC ACID EXCESSES  
TYNDALL EFFECT  
GRANULOMA

Philippe Deprez & Evgenyia Ranneva

## ABSTRACT

Hyaluronidase is an enzyme that specifically dissolves hyaluronic acid polymers. In the past it has been largely used for undoing cellulitis fibrosis and more recently, for dissolving hyaluronic acid filler excesses of granulomas. The use of hyaluronidase is very simple and comprises the injection of a sterile dissolution of the hyaluronidase powder directly inside the problem area to be treated.

An allergy test is absolutely essential before every injection session, since hyaluronidase is an enzyme, an exogenous protein. Results can be seen very quickly and are definitive.

Yaluronic acid is a natural polymer actually considered as the simplest and safest filler agent. Cross-linked hyaluronic acid is widely used to treat facial wrinkles and folds, augment the lips, and for volumisation in the face, hands and body. Non-cross-linked hyaluronic acids are used in order to refill and rehydrate the dermis, and are also often associated with biorevitalisation actives in order to combine the hydration effect with stimulation of the normal metabolic skin processes, or to help other molecules to widely diffuse into the dermis or increase the penetration of drugs.

The side-effects of cross-linked hyaluronic acid have mainly been described in terms of over-correction, infection or granuloma. Other rare cases have been described, including local necrosis as a result of vascular compression or lung embolism after vaginal injection. All kinds of side-effects are uncommon, making hyaluronic acid safe to use as an office treatment.

Hyaluronidase is a specific enzyme, able to cut the hyaluronic acid polymer; it is used in cases of over-correction, fibrosis, granuloma, and also for reducing the risk of an eventual vascular compression, which could lead to skin necrosis.

## Granuloma

Hyaluronic acid is a polymer formed by thousands of alternative units of N-acetylglucosamine and glucuronic acid. It is therefore a heteropolysaccharide. Hyaluronic acid is usually used in the cross-linked form, mainly with the aim to correct volume; the face, lips, hands and body can be treated. Any excess of prod-

uct gives an unaesthetic result, but fortunately, slowly disappears within a few months owing to the activity of natural hyaluronidase enzymes. As hyaluronic acid is a natural polymer, widely present in human tissues and especially the skin, it is usually not recognised as a foreign body. In certain cases, nevertheless, the body considers injected hyaluronic acid (or some impurities of it) as a foreign molecule, and can induce an immune reaction that can appear after even after a number of years, as well as the formation of granuloma. In this case, the symptoms of inflammation are visible (rubor, tumour, dolor, calor) and sustained. The granuloma may persist for a long time before natural resolution or surgical extraction. Native hyaluronidase, present in the dermis, will sometimes have no access to the hyaluronic acid when it is considered a foreign body, and the product could be slowly eliminated through an inflammatory reaction and phage cells.

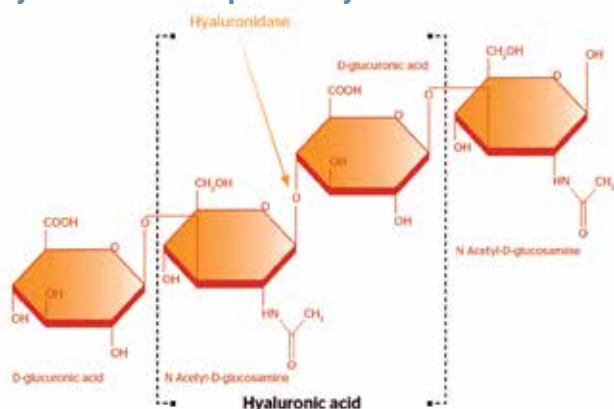
## Hyaluronidase

Hyaluronidase is a natural enzyme produced by the body, which decreases fibrosis and, in some cases, symptoms of inflammation. It helps spermatozooids to penetrate the ovule, for example. On the other hand, some cancer cells also use hyaluronidase to aid diffusion into tissues. Some animals inject hyaluronidase together with venom in order to increase the diffusion of toxins.

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Hyaluronidase is able to cut the long hyaluronic acid polymer into oligomers, which will no longer be considered a foreign body by the immune system. The activity of the enzyme is very specific, hydrolysing the

## Hyaluronidase specificity



links between N-acetyl-D-glucosamine and D-glucuronic acid.

There is, therefore, no way to hope that hyaluronidase could aid in cases of excess injections of another kind of molecule (e.g. polylactic acid, collagen, silicone), or in cases of immune reactions to these products. Hyaluronidase is usually presented in a lyophilised form, 1500 IU to be mixed with a sterile saline solution. It does not contain conservative products and must be used immediately after reconstitution.

## Allergy to hyaluronidase

Hyaluronidase has been used for many years. The lead author first used the product in 1977 in order to undo cellulitis fibrosis. It is also widely used in anaesthesia as it helps local anaesthetic to spread to the tissues. Reports of sensitivity or allergy to hyaluronidase are rare, and are usually related to ophthalmic surgery using retrobulbar or peribulbar anaesthesia. An immediate allergic reaction (anaphylactic shock) has been described in one case of epidurally administered hyaluronidase<sup>1</sup>. However, most patients will usually develop an allergy only after having received at least one injection in the past, allowing a sensitivity to develop and express during further injections. Nevertheless, it is theoretically possible that any type of allergy could occur during the first injection, making a test before every injection of hyaluronidase necessary.

Allergic reactions are considered as either type I or type IV hypersensitive reactions, having an immediate onset (anaphylactic shock), an intermediate (after a few hours), or a delayed onset (a few days or weeks after the injection). Type I immediate reactions are particularly marked by oedema,

rash, itching, pain, respiratory distress, nausea, vomiting, and hypotension. These reactions require immediate medical treatment. Immediate reactions such as anaphylactic shock, general urticaria and respiratory distress, usually appear after intravascular injection, and have been described during hyaluronidase-chemotherapeutic agent injections for cancer. Clinical symptoms of the allergic reaction are efficiently treated with corticoid injection, eventually associated with adrenaline and antihistamine. Symptoms of low blood pressure should be immediately treated using a pressor agent.

After repeated subcutaneous injection, the occurrence of a transitory delayed or intermediate (24 hours) reaction is not uncommon and takes the appearance of large, reddish, swollen and itchy macules that disappear after a few days without any treatment. Topical corticoid cream can also be used during the active period of allergic reaction. Furthermore, hyaluronidase injections have to be entirely avoided in such cases.

Intradermal tests are more sensitive than prick tests and are important to gauge a potential allergy to hyaluronidase. Prick tests and blood immunoglobulin E (IgE) levels are not always sufficient to predict an allergic reaction. Performing this test is quite simple: 1500 IU of hyaluronidase are diluted in 8–10 ml saline solution, with each ml containing up to 150 IU. Then, 0.1 ml of this dilution is injected subcutaneously to the forearm. The patient is kept in the clinic for an average of 60 minutes. Any reaction (e.g. itching, swelling, redness) at the injection point signifies that the patient should not receive treatment. A subcutaneous test is recommended for all patients prior to the injection of hyaluronidase.

## Hyaluronidase for reducing the risk of necrosis after an excess of hyaluronic acid

Hyaluronidase, by quickly breaking down the hyaluronic acid polymer, is able to reduce the risk of skin necrosis secondary to vascular compression if injected early, according to the medical literature<sup>2–4</sup>. Unfortunately, injection after 24 hours has been shown to be rather inefficient. Kim et al<sup>2</sup> experimented using intra-arterial injection of hyaluronic acid in a rabbit ear, followed by an injection of hyaluronidase both 4 and 24 hours later. A late injection did not reduce the size of necrosis, while an earlier injection significantly reduced the size of skin necrosis. Hyaluronidase should therefore be immediately injected

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**Figure 1** Intradermal injections of cross-linked hyaluronic acid

in cases of symptoms suggesting vascular compression .

### Hyaluronic acid filler excesses

The injection of hyaluronidase fortunately erases any cross-linked hyaluronic acid very quickly, but the speed

will generally depend on the strength of the cross-linking. in these cases, the delay between the injection of hyaluronic acid and hyaluronidase is not relevant® even when injected years later, hyaluronidase is able to cut the polymer. Reports show that hyaluronidase is able to dissolve hyaluronic acid injections in the periorbital area, even 5 years after the original injection. Again, intradermal testing should be carried out prior to injection. The task is to evaluate the volume and concentration of hyaluronidase to be injected in order to dissolve the excess only, without dissolving every hyaluronic acid molecule outside the injection area. There is no known consensus on this point, but it is known that some hyaluronic acids are more resisting to hyaluronidase than others.

Hyaluronic acid excesses can occur after superficial injections (mesotherapy-like injections) of cross-linked hyaluronic acid (Figure 1). in such cases, one injection of one drop of hyaluronidase (1500 ui diluted in 4 ml saline solution), directly inside the tumefaction induced by the hyaluronic acid, can quickly resolve the problem, no matter what the delay is between hyaluronic and hyaluronidase injections. Hyaluronic excesses usually occur after injections to periorbital wrinkles or correction to under-eye circles, giving the puffy eye appearance seen in Figures 2 and 3. in the case of Figure 4, a cross-linked hyaluronic acid

had been injected into the under-eye circles 2 years previously. The patient was informed that the hyaluronic acid had no tendency to disappear and of any surgical possibility of erasing the puffiness to the lower eyelids. injection of hyaluronidase was therefore decided on, using an ovine lyophilised hyaluronidase, with a dilution of 4ml saline solution for 1500iu. After an allergy test showing a lack of immediate reactivity in the patient, three injections points of 0.1 ml each were carried out on each side. As the product is presented in a 1 ml syringe, with a 32 G needle, retro-injections should be performed directly inside the area showing the excess of hyaluronic acid. injections here should be quite deep, as hyaluronic injections to this area are usually performed close to the bone. no side-effects, except transitory ecchymoses and local oedema, should be expected in normal conditions.



**Figures 2 and 3** - IntraleSIONal injections of hyaluronidase



**Figure 4** - Puffy eyes as a result of hyaluronic acid excess



**Figure 5** - Result following correction with hyaluronidase

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The result of the injection began to be visible after 1 hour, when the patient was allowed to leave the clinic. Figure 5 shows the definitive result after day 3—a complete disappearance of injected hyaluronic acid and a return to the original state with wrinkles and under-eye circles. A new injection of hyaluronic acid was carried out 2 weeks after the hyaluronidase treatment in order to fill this area without excess. no problems were experienced as a result of the corrective injection. Many cases of cross-linked hyaluronic acid excesses have also been witnessed in lip augmentation.

The authors have only had one experience of general hyaluronic acid excess in this area, which was sent to the clinic by a colleague. The injection of hyaluronidase allowed for the correction of the problem over a few days, and without side-effects.

### Tyndall effect

Superficial injections of hyaluronic acid can give the skin

a different colour around the entire injection area compared with normal colouring. The skin may appear blueish, but in this case the resulting colour was different (Figure 6). cross-linked hyaluronic acid had been injected a few months previously and the patient, even if happy to see the disappearance of circles around the eyes, wanted the change in colour to be removed. Hyaluronidase was injected, very superficially, in order to place the product exactly inside the non-accepted coat of hyaluronic acid. Hyaluronidase was diluted in 4 ml saline solution and, after an intradermal allergy test, 0.2 ml were released in three retro-injection lines: 75iu of hyaluronidase were therefore injected on each side. Figure 7 shows the result 30 minutes after the superficial injection. A further correction can be carried out, but the delay for a new correction has not yet been defined. The authors prefer to wait for at least 1 week between hyaluronidase injection and a new hyaluronic acid implant.



Figure 6 Tyndall effect



Figure 7 Correction of Tyndall effect following treatment with hyaluronidase

“Hyaluronidase is a simple treatment that gives an immediate result, rubbing out excesses and even granuloma.”

cross-linked hyaluronic acid injection to the malar area a few months previously, and without any problem. A strong inflammatory reaction associated with a local granulomatous reaction appeared a few days after a thermogenic radiofrequency treatment. As visible in Figures 8 and 9, the whole area was swollen and the entry points of the previous implant appeared swollen and red. The patient was treated with three careful successive injections of low doses of ovine hyaluronidase, with a complete return to her normal appearance after the third injection. no side-effects were noted immediately or even some weeks after the injections.

## Conclusions

Cross-linked hyaluronic acid fillers are actually widely used in aesthetic medicine. Hyaluronic acid is considered a very safe implant but nevertheless, can result in some side-effects. Hyaluronidase is a simple treatment that gives an immediate result, rubbing out excesses and even granuloma. it is also used for melting fibrotic areas. Hyaluronidase should therefore be included in our therapeutic armamentarium against the side-effects of hyaluronic acid. The main concern for using hyaluronidase is a possible allergic reaction, making an intradermal test necessary before every treatment.



Figure 8 - Granuloma of hyaluronic acid appeared after local thermogenic treatment



Figure 9 - Result after treatment with three injections of low-dose ovine hyaluronidase

## Granuloma

Granuloma, a reddish swollen tumour on the site of injection of hyaluronic acid, is secondary to an immune reaction against the polymer. The patient in Figure 8 received a

## Key points

- Hyaluronidase is an enzyme used specifically to treat hyaluronic acid and filler excesses
- All patients should be allergy tested prior to the use of hyaluronidase
- Hyaluronidase has been used for many years and can provide very fast and definitive results

## References

1. Lee HK, Choi EJ, Lee PB, Nahm FS. Anaphylactic shock caused by the epidurally-administered hyaluronidase. *Korean J Pain* 2011; 24(4): 221-5
2. Kim DW, Yoon ES, Ji YH, Park SH, Lee BI, Dhong ES. Vascular complications of hyaluronic acid fillers and the role of hyaluronidase in management. *J Plast Reconstr Aesthet Surg* 2011; 64(12): 1590-5
3. Glaich AS, Cohen JL, Goldberh LH. Injection necrosis of the glabella: protocol for prevention and treatment after use of dermal fillers. *Dermatol Surg* 2006; 32(2): 276-81
4. 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
5. Fabi SG, Goldman MP. Hand Rejuvenation: A Review and Our Experience. *Dermatol Surg* 2012; [Epub ahead of print]
6. Andre P, Levy P. Hyaluronidase offers an efficacious treatment for unaesthetic hyaluronic acid overcorrection. *J Cosmet Dermatol* 2007; 6(3): 159-62
7. Dayan SH, Arkins JP, Mathison CC. Management of impending necrosis associated with soft tissue filler injections. *J Drugs Dermatol* 2011; 10(9): 1007-12
8. Kim TW, Lee JH, Yoon KB, Yoon DM. Allergic reactions to hyaluronidase in pain management -A report of three cases-. *Korean J Anesthesiol* 2011; 60(1): 57-9
9. Hirsch RJ, Brody HJ, Carruthers JD. Hyaluronidase in the office: a necessity for every dermasurgeon that injects hyaluronic acid. *J Cosmet Laser Ther* 2007; 9(3): 182-5
10. Soparkar CN, Patrinely JR, Tschen J. Erasing restylane. *Ophthal Plast Reconstruction. Surg* 2004; 20(4): 317-8