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<th>The Use of Hyaluronidase in Aesthetic Practice</th>
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The Use of Hyaluronidase in Aesthetic Practice

Background

Hyaluronic acid based dermal fillers are the most commonly used in the aesthetics market. It is a glycosaminoglycan and a chief component of the extracellular matrix, it is mainly responsible for maintaining hydration in the dermis. It is a linear polysaccharide chain with the alternating monosaccharides d-glucuronic acid and N-acetyl-d-glucosamine. Hyaluronidases are enzymes (endoglycosidases) that are able to depolymerise hyaluronic acid leading to its degradation. They are licensed in the UK for enhancing permeation of subcutaneous or intramuscular injections, local anaesthetics and subcutaneous infusions and to promote resorption of excess fluids and blood. However there is now much evidence for their off-label use in aesthetic medicine for dealing with vascular compromise (due to inadvertent intravascular injection or external compression) caused by injection of hyaluronic acid filler, over-correction, asymmetry, lumps and nodules.

There are several sources of hyaluronidase and they are generally divided into 3 subgroups (Meyer), mammalian (obtained from the testis), hookworm/leech and microbial although recombinant human hyaluronidase is now available (Hylenex, from Halozyme Therapeutics, San Diego, California) which has a purity of 100 times higher than some currently used Bovine preparations. There are no long term data for this product yet but it is likely to have a lower proportion of allergic reactions.

This guidance refers to the use of Hyalase (Wockhardt) which is readily available in the UK as a 1500 unit ampoule of powder for reconstitution and is of ovine (sheep) origin.

Off-label use of hyaluronidase

Although hyaluronidase is not licensed for the use in correcting problems with dermal filler injections and off-label promotion is not allowed by Article 87 of Directive 2001/83/EC, its use is allowed provided the patient’s best interest and autonomy are respected and forms part of the informed consent (MHRA, 2009).

What should be treated?

Vascular compromise as a result of hyaluronic acid filler injection should be treated immediately (refer to Aesthetic Complications Expert Group, Necrosis guidance). Signs of impending necrosis include pain, prolonged blanching (reticulated white or dusky appearance of the skin) and coolness of the skin. Hyaluronidase should be administered as soon as this complication occurs, there is good evidence that tissue necrosis will be prevented or be less severe the sooner the hyaluronidase is injected.

The Tyndall effect refers to the scattering of light that may be seen in some patients after injection of hyaluronic acid resulting in a bluish hue of the skin (refer to Aesthetic Complications Expert Group, Tyndall’s effect guidance). It is often caused by injecting too
superficially, placing large boluses of product in one area or using an inappropriate product for the area treated. It is most commonly seen in the sub ocular region. By degrading the hyaluronic acid using hyaluronidase, this problem can usually be corrected.

Overcorrection or misplacement of hyaluronic acid filler can be successfully treated with hyaluronidase although this is often caused by poor injection technique or poor choice of product for a particular area.

Lumps or nodules that may appear several months after the initial treatment may be amenable to hyaluronidase (refer to Aesthetic Complications Expert Group, Delayed Onset Nodules guidance). It is important to remember that hyaluronidase is used to help diffuse fluids intradermally and for hypodermoclysis so if the nodule is thought to be infective, it is important to administer antibiotics to prevent further spread of infection (refer to Aesthetic Complications Expert Group, Infection guidance).

**Storage and reconstitution**

It is recommended that hyaluronidase should be stored at cool temperatures (2-8°C) as this guarantees the quality of the product over a long period. If storage is at room temperature (25°C), the stability is only guaranteed for 12 months.

Hyalase® may be reconstituted with either saline or water for injection. Reconstitution with saline tends to produce less stinging so is recommended. Although local anaesthetics may be used to reconstitute the product, as the enzymatic action of hyaluronidase can be affected by pH, care should be made with diluents. Hyaluronidase is indicated to improve permeation of subcutaneous products so the injection of local anaesthetic as a diluent may lead to wider spread and increased systemic absorption. For this reason, this guidance does not advocate the addition of local anaesthetic.

**Reconstitution instructions:** Open a 10ml ampoule of saline and add 1ml of saline to the opened ampoule of Hyalase®, ensure the powder is fully dissolved (draw up and expel the syringe a couple of times to ensure complete mixing). Aspirate the 1ml of saline with the reconstituted Hyalase® and re-introduce it into the ampoule of saline. Agitate the ampoule to ensure the Hyalase® is mixed throughout the whole volume of saline. This now gives a concentration of 150 Units/ml. The reconstituted solution can now be drawn up in a 0.3ml or 0.5ml syringe with a 27G or 30G needle. Each 0.01ml graduation represents 1.5 Units of Hyalase®.

**Dosages of hyaluronidase**

Hyaluronidase may degrade the body’s natural hyaluronic acid in preference to foreign hyaluronic acid filler that has been injected and specifically cross-linked to prevent its natural breakdown. The dosage required is dependent on several factors relating to the particular hyaluronic acid filler, whether it is particulate or non-particulate, the amount of cross-linking and the concentration of hyaluronic acid. It is therefore recommended to treat to effect rather than absolute dosage (injecting as much hyaluronidase as required to obtain
the desired effect), however the table below will give an indication of how much will be required:

<table>
<thead>
<tr>
<th>Region</th>
<th>Hyaluronidase (Units)</th>
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<tr>
<td>Nasal and perioral skin</td>
<td>15-30\textsuperscript{9,10}</td>
</tr>
<tr>
<td>Periorbital</td>
<td>30\textsuperscript{10}</td>
</tr>
<tr>
<td>Infraorbital</td>
<td>10-15\textsuperscript{11}</td>
</tr>
<tr>
<td>Lower lid</td>
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**Intradermal patch testing**

Although there is some controversy between professionals on the benefit of test patching, after reviewing the evidence the Aesthetic Complications Expert Group recommends the use of a test patch except when the indication is for vascular compromise and a delay could result in further harm to the patient. An intradermal injection of 4-8 Units of hyaluronidase in the forearm is advised and observing the results after 20-30 minutes\textsuperscript{13}. A positive reaction is identified by a weal and itching observed at the injection site, minor inflammation and erythema can occur as a normal finding. However, other studies recommend a higher test dose of 20 Units of hyaluronidase as a positive reaction at lower doses may not be recognised\textsuperscript{14}.

**Drug interactions**

The most common interactions occur with furosemide, benzodiazepines, phenytoin, dopamine and α-adrenergic agonists so it is important to obtain a medical history. Although interactions are not particularly significant, it is best to avoid if possible. Several drugs act as antagonists to hyaluronidase including anti-inflammatory drugs (such as ibuprofen, aspirin, diclofenac), anti-histamines, mast cell stabilisers, Vitamin C, flavonoids and anti-oxidants\textsuperscript{9}.

**Administration**

Prior to injection, the area should be inspected and palpated and marked out if needed. The area should be sterilised using an appropriate skin solution and the procedure should be carried out using as close to aseptic technique as possible. A 27G or 30G needle with an appropriate length to treat the depth of the area should be used. Administration should be extremely accurate and limited to the affected area. In the case of nodules, they should be injected directly and for product that has been injected into the superficial dermis, injections should be placed immediately into and below the product\textsuperscript{15}. For vascular compromise, serial puncture should be used to inject hyaluronidase along the course of the vessel. The needle should be perpendicular to the skin and several injections are often necessary. During and after the procedure, the treated area should be massaged rather vigorously to optimise the result and aid mechanical breakdown. Due to the spreading effect of hyaluronidase, treatment should not be performed in an area where botulinum toxin has been performed within the last 48 hours or an area of skin infection.
Results are often seen almost immediately although for denser, more cross-linked products it may take 48 hours for the effects to be seen. A review appointment at 2-3 weeks should be offered and further treatment offered at this point if needed.

Following administration of hyaluronidase, the patient should be observed for 30 minutes to ensure no adverse reactions occur and aftercare given. In the event of any delayed reaction to the treatment, the patient should be seen at the earliest opportunity.

**Complications**

The most common complication following the administration of hyaluronidase is an allergic reaction. Depending on the area treated, different allergic responses have been described. Local reactions are by far the most common and according to the clinical studies occur at a frequency of 0.05% to 0.69%\(^3\) although these figures are likely to be a little lower due to under reporting. Signs include oedema, erythema, pain and itching. Urticaria and angioedema have been reported in less than 0.1% of cases\(^16\). Anaphylaxis has occurred with the use of hyaluronidase when high doses have been administered and with intravenous administration (refer to Aesthetic Complications Expert Group, Anaphylaxis guidance). Type I (IgE mediated) and Type IV (mediated by T-cells) hypersensitivity reactions have occurred as a result of hyaluronidase treatment. Following the use of hyaluronidase the patient should be observed for 30 minutes in a clinical environment and given appropriate aftercare information (Appendix 2).

Unless there is a past medical history of allergic reaction or anaphylaxis to hyaluronidase, previous history of allergy seems unrelated for the administration of hyaluronidase\(^17\) and it can be safely performed.
Appendix 1: Consent for treatment with Hyalase® to dissolve hyaluronic acid dermal fillers

Hyaluronic acid (HA) fillers are sterile gels consisting of non-animal stabilised hyaluronic acid for injection into the skin to correct facial lines, wrinkles and folds, for lip enhancement and for shaping facial contours.

Occasionally these fillers need to be dissolved when the aesthetic treatment has not produced the desired outcome or there is a possibility of vascular occlusion or impending necrosis (tissue death) which could lead to compromise of healthy tissue.

Hyalase® (hyaluronidase 1500 units) has an off-license use in aesthetic medicine and except in the case of emergency administration requires the patient to undergo a skin patch test at least twenty minutes prior to the procedure being undertaken. The skin patch test is carried out by injecting Hyalase® into the subcutaneous tissue of the forearm and observed for signs of reaction (i.e. hives or wheals). If a positive patch test result is observed, treatment with Hyalase® cannot be carried out. Erythema or redness and slight vasodilation may be expected.

Hyalase® is an enzyme which breaks down hyaluronic acid fillers, but it can also break down naturally occurring hyaluronic acid present in the body, the results can be unpredictable and the effect dramatic. I understand that there will be loss of volume and there can be some skin laxity which in itself may not provide a good aesthetic result. Although some of the effects can be immediate, I understand that it can take up to 14 days for the final results to be seen and the treatment may need to be repeated.

Hyalase® administration can result in anaphylaxis (a severe allergic reaction which in itself is life threatening and requires immediate medical attention) and I understand this and have been given full counselling and the opportunity to discuss the treatment with Hyalase®, conservative treatment options or leaving the dermal filler to break down naturally which may take several months dependent on the type of filler used and the area treated.

The use of and the indications for the administration of Hyalase® have been explained to me by my practitioner and I have had the opportunity to have all questions answered to my satisfaction. After the treatment some other common injection-related reactions might occur. These reactions include redness, swelling, pain, itching, bruising and tenderness at the injection site. They have generally been described as mild to moderate and typically resolve spontaneously a few days after injection. Bruising may occasionally be more significant.

I acknowledge that I will have to remain at the clinic for thirty minutes after the procedure so that I can be observed by the medical staff and that I may need to return to the clinic 2-3 weeks after treatment to assess if further Hyalase® is to be administered.

I have answered the questions regarding my medical history to the best of my knowledge. I have also received the aftercare information and its contents have been explained to me and I will follow the advice given.

I consent to being treated with Hyalase®

__________________________   _______________________
Name                          Date

__________________________   _______________________
Signature                    Practitioner
Appendix 2: Hyalase® (Hyaluronidase) Injection Aftercare

Keep this aftercare leaflet safe and present it to the treating physician in the event of an adverse reaction

Hyalase® is an enzyme which breaks down hyaluronic acid fillers, but it can also break down naturally occurring hyaluronic acid present in the body. The results can be unpredictable and the effect dramatic with possible loss of volume and some skin laxity. Although some of the effects can be immediate, it can take up to 2 weeks for the final results to be seen and the procedure may need to be repeated.

Hyalase® administration can result in anaphylaxis (a severe allergic reaction) which in itself is life threatening and requires immediate medical attention. Symptoms of a severe allergic reaction can include shortness of breath, wheezing, coughing, difficulty swallowing, swelling of the tongue, eyelids, lips, hoarseness of the voice, stomach pain, nausea or diarrhoea.

If you have any of the above symptoms please report to your nearest Accident and Emergency Department or call 999 for an ambulance.

After the procedure some other common injection-related reactions might occur. These reactions include redness, swelling, pain, itching, bruising and tenderness at the injection site. They have generally been described as mild to moderate and typically resolve spontaneously after a few days after injection. Bruising may occasionally be more significant.

If you have any concerns following treatment, do not hesitate to contact us on <telephone number>. If this is outside of normal hours, please leave an answerphone message and we will normally get straight back to you.

I have been treated with Hyalase® (Hyaluronidase, 1500u reconstituted with 10mls of saline) to dissolve a hyaluronic acid dermal filler. A skin patch test was administered to the left/right (delete as appropriate) forearm. No sign of an allergic reaction was noted and the procedure undertaken. Following injection, I was monitored for 30 minutes within the clinic.

Date of procedure: Amount administered:

Area treated:
References


3. Maurizio Cavallini, MD; Riccardo Gazzola, MD; Marco Metalla, MD; and Luca Vaienti, MD. The Role of Hyaluronidase in the Treatment of Complications From Hyaluronic Acid Dermal Fillers. Aesthetic Surgery Journal 33(8) 1167–1174

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