The Use of Hyaluronidase in Aesthetic Practice

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Background

Hyaluronic acid based dermal fillers are the most commonly used in the aesthetics market[1]. A glycosaminoglycan and a chief component of the extracellular matrix, it is mainly responsible for maintaining hydration in the dermis. Hyaluronic acid is a linear polysaccharide chain with the alternating monosaccharides d-glucuronic acid and N-acetyl-d-glucosamine[2].

Hyaluronidases are enzymes (endoglycosidases) that can depolymerise hyaluronic acid leading to its degradation[3] by hydrolysing the disaccharides at hexosaminidic beta (1-4) linkages[4]. Hyaluronidase is 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[5]. There is considerable evidence for the off-label use in aesthetic medicine for dealing with vascular compromise (due to inadvertent intravascular injection or external compression)[6], over-correction, asymmetry, lumps and nodules[7], caused by the injection of hyaluronic acid filler.

There are several sources of hyaluronidase and they are generally divided into 3 subgroups[8]; mammalian (obtained from the testis), hookworm/leech and microbial. Recombinant human hyaluronidase is now available (Hylenex, from Halozyme Therapeutics, San Diego, California) which has a purity of 100 times higher than some currently using Bovine preparations[9]. There is no long-term data for this product yet, but it is likely to have a lower incidence of allergic reactions.

Hyaluronidase has immediate effect and has a half-life of 2 minutes[10] with duration of action typically 24-48 hours[11]. Despite such a short half-life, the effectiveness is much longer. This may be due to only a few units of hyaluronidase being required to have a clinically significant effect so even when most of it is degraded, it continues to act. Additionally, the initial action of hyaluronidase may break cross-links in the hyaluronic acid dermal filler so that it behaves like native hyaluronic acid in the skin which has a half-life of 24 hours[12].

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).

Indications for the use of hyaluronidase in aesthetic practice

(1) Vascular Occlusion

The incidence of impending necrosis following dermal filler treatment has been estimated at 0.001% (1 in 100,000 cases)[7]. Vascular compromise due to hyaluronic acid filler injection should be treated immediately (refer to Aesthetic Complications Expert Group, Impending Necrosis guidance). Normal skin should be non-discoloured and warm with a capillary refill time of 1-2 seconds whereas arterial compromise will have a slow capillary refill time and dusky or blue-grey-black appearance and venous insufficiency will have a fast capillary time and bluish discolouration[13]. Signs of impending necrosis also includes pain and coolness of the skin. Hyaluronidase should be administered as soon as this complication occurs (<4 hours)[4,14]. There is good evidence that tissue necrosis will be prevented or be less severe the sooner the hyaluronidase is injected[6] and if treatment is

administered within 48 hours[15]. However, a small animal-based study tested this theory and found that injecting hyaluronidase at 24 hours failed to afford any benefit[16].

(2) Blindness

Blindness due to periocular embolism of hyaluronic acid is instant and associated with excruciating ocular pain and the retinal circulation needs to be restored within 60-90 minutes if the retina is to survive. Blindness is a medical emergency and the patient should be transferred urgently to the nearest hospital eye department (Refer to Aesthetic Complications Expert Group, Blindness guidance). Retrobulbar injection of hyaluronidase (150-200 units in 2-4ml of diluent) into the inferolateral orbit[17] may be considered by practitioners with appropriate experience and competence whilst awaiting ambulance transfer. Treatment of blindness is rarely successful[17].

(3) Tyndall Effect

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 and most commonly seen in the sub ocular region. The problem can be resolved using hyaluronidase (Refer to Aesthetic Complications Expert Group, Tyndall's effect guidance).

(4) Unacceptable Cosmetic Outcome

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 indication. If hyaluronic acid is present then hyaluronidase is effective and Restylane® has been successfully removed 63 months post treatment[18].

(5) Delayed Onset Nodules

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. If the nodule is inflammatory, it is important to prescribe antibiotics for one week before administering hyaluronidase to prevent potential dissemination of infection.

(6) Allergic or Immunogenic Reaction to the Hyaluronic Acid Dermal Filler

In cases where an allergic, immunogenic or sensitivity reaction occurs and does not settle spontaneously within an acceptable (to the patient) time or with a short course of anti-histamines or systemic corticosteroids, then removal with hyaluronidase is appropriate. If the reaction is considered moderate or severe, oral corticosteroids should be taken when using hyaluronidase, because the treatment may lead to initial worsening of symptoms as more antigen is exposed to the patient as the hyaluronic acid is broken down.

Storage and reconstitution

It is recommended that hyaluronidase should be stored at cool temperatures (2-8^{o}C) as this guarantees the quality of the product over a long period. If storage is at room temperature (25^{o}C), the stability is only guaranteed for 12 months. Once the ampoule is opened, Hyalase® must be used immediately and any unused contents discarded (Hyalase® SPC).

Hyaluronidase may be reconstituted with either saline or water for injection (Hyalase® SPC). Saline is less painful on injection and is recommended for this reason. Although unlicensed for this purpose, bacteriostatic saline is often preferred for its additional anaesthetic properties. Although local anaesthetics may be used to reconstitute the product, as the enzymatic action of hyaluronidase can be affected by pH[7], caution should be applied to the choice of diluent. There is little evidence to support the addition of local anaesthetic agents to hyaluronidase[18]

and when combined may lead to wider spread and increased systemic absorption of anaesthetic and potential complications.

The volume of diluent used will depend on the indication and surface area to be treated and a range of 1-10mls has been evidenced in clinical practice and published papers. Larger volumes of dilution are recommended when smaller amounts of Hyalase® are required to allow more precise dosing. Smaller volumes should be used in the case of vascular occlusion or when large volumes of dissolution are required to allow a higher concentration of Hyalase® in a smaller area. Once the volume of diluent has been chosen, add 1ml of diluent 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® adding this to the remaining diluent. Agitate the solution to ensure the Hyalase® is mixed throughout the whole volume. The reconstituted solution can now be drawn up in a syringe and injected where needed. The number of units to be injected can be calculated by:

Volume to inject (mls) = $\frac{\text{Number of units required (units)}}{\text{Total number of units (1500 units)}}$ X Volume of diluent (mls)

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[13]. The dosage required is dependent on several factors relating to the hyaluronic acid filler; whether it is particulate or non-particulate, the amount of cross-linking and the concentration of hyaluronic acid[19]. Different hyaluronic acid fillers have differing physical properties that influence their degradation by hyaluronidase in a time and dose dependent manner. A study by Rao et al[20] demonstrated Restylane® dissipated most and Belotero® least[21]. However a more recent study has shown that Belotero® was the fastest to dissolve and Juvederm® Voluma® and Restylane® Lyft were the slowest[19] with the authors concluding that a high concentration of hyaluronic acid, larger particle size and increased cross-linking increases the durability of the filler[19].

The literature offers examples of widely divergent doses however it is recommended to treat to effect rather than absolute dosage (injecting as much hyaluronidase as required to obtain the desired effect)[13].

(A) Dosages for all indications except vascular occlusion

Although the amount injected should be titrated to clinical effect[13], the following table[3] offers a guide to actual dosages used in published articles:

Region	Hyaluronidase (Units)
Nasal and perioral skin	15-30[22,23]
Periorbital	3-4.5[24]
Infraorbital	10-15[25]
Lower lid	1.5[26]

A consensus opinion in the literature states 5 units of hyaluronidase is needed to break down 0.1ml of 20mg/ml hyaluronic acid[10] although there is quite a range and Woodward et al[21] describe 30 units to dissolve 0.1ml. A further study showed no statistical difference between the use of 20 or 40 units of hyaluronidase in degrading 0.2mls (4 to 6mg of hyaluronic acid) of various fillers[19].

Treatment results may be assessed from 48 hours[4] and may be repeated at 48 hour or longer intervals. The degree of further treatment will depend upon indication, risks versus benefits, side effects from treatment and patient and practitioner satisfaction.

(B) Dosages for vascular occlusion

In the event of a suspected vascular obstruction, a high dose pulsed protocol[27] should be adopted. Large volume of hyaluronidase (450-1500 units) should be infiltrated over the entire area including the course of the vessel[4,13,28]. Perivascular hyaluronidase will permeate vascular walls[4,29]. Massage the area to promote diffusion and mechanical breakdown. Observe and reassess capillary refill after 60 minutes, if there is still vascular compromise, repeat treatment at hourly intervals for up to 4 cycles[30]. The patient should be kept under observation in clinic for any adverse reactions and provided with written aftercare and advice. When anaphylaxis occurs, it is usually within minutes but there have been cases where there has been a delayed onset. All patients should be given appropriate aftercare advice, warned about the symptoms of an allergic or anaphylactic response and how to seek appropriate medical attention. Daily follow up should occur until there is satisfactory resolution.

Vascular occlusion is often immediate; however, the Aesthetic Complications Expert group have many reported cases when the symptoms of ischaemia start several hours or even days later. This may be due to the dermal filler being intravascular but trapped at a bifurcation or branch point only to dislodge at a later point to cause an occlusion[29]. Alternatively, if the venous return is compromised by secondary swelling following injection of hydrophilic dermal filler this can cause increased pressure in the arterial tree and a reduction in tissue perfusion.

Intradermal patch testing

A test patch should be performed[31] 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 has been advocated and observing the results after 30 minutes[32]. However, it is recommended that a higher test dose of 20 Units of hyaluronidase is used as a positive reaction at lower doses may not be recognised[33].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.

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[3]. Higher doses or repeated treatments may be required with concomitant use of these medicines[28]. Where possible, patients should be advised to stop taking non-prescribed medication in advance of treatment.

Administration

Prior to injection, the area should be inspected, palpated and marked out if needed. The area should be cleansed then disinfected using an appropriate skin solution and the procedure should be carried out using an aseptic technique. A 27G or 30G needle with an appropriate length to treat the depth of the area should be used. Administration should be accurate and limited to the affected area. Depth may be difficult to assess on palpation therefore injections should cover the upper and lower borders of the product that has been injected.

Nodules, and product that has been injected into the superficial dermis should be injected directly, injections should be placed immediately into and below the product[34]. For vascular compromise, serial puncture should be used to inject hyaluronidase along the course of the vessel[4] and covering the affected area. 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 unless there is a vascular occlusion and the risks outweigh the benefits.

Follow Up

Results are often seen almost immediately although for denser, more cross-linked products it may take 48 hours for the effects to be seen. Consent should be obtained for the practitioner to inform the patient's General Practitioner. A review appointment should be offered and further treatment offered at this point if needed.

Following administration of hyaluronidase, the patient should be observed for 60 minutes to ensure no adverse reactions occur and aftercare instructions given. In the event of any delayed reaction to the treatment, the patient should be seen at the earliest opportunity.

Complications

Bruising[35] and swelling post-treatment are common[14]. The most serious 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[36]. 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 because of hyaluronidase treatment. Following the use of hyaluronidase, the patient should be observed for 60 minutes in a clinical environment and given appropriate aftercare information (Appendix 2).

A history of allergic reaction to wasp or bee stings represents an increased risk of allergic reaction to hyaluronidase and should be considered as a relative contra-indication[37,38] as the venom of stinging insects may contain hyaluronidase and this mechanism may be the source of sensitisation in affected individuals[13]. Unless there is a past medical history of allergic reaction or anaphylaxis to hyaluronidase or insect bites, previous history of allergy seems unrelated for the administration of hyaluronidase[39] 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 ____ minutes after the procedure so that I can be observed by the medical staff and that I may need to return to the clinic ____ days/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 _____ Units of Hyaluronidase (Hyalase®) reconstituted in ____ mls of Saline / Water (delete as applicable) to dissolve a hyaluronic acid dermal filler. A skin patch test was administered to the left/right (delete as applicable) forearm. No sign of an allergic reaction was noted and the procedure undertaken. Following injection, I was monitored for 60 minutes within the clinic.

Date of procedure: Amount administered:

Area treated:

The Aesthetic Complications Expert Group protocol for the administration of Hyalase®

VASCULAR OCCLUSION

Reconstitute Hyalase® in 1-5ml of solution (The ACE Group recommends dilution in 2mls bacteriostatic saline)

↓

Infiltrate 450-1500 units of Hyalase® over the entire area including the course of the vessel by serial puncture

↓

Massage and apply heat

↓

Reassess after 1 hour to ensure capillary refill <4 seconds

↓

Resolved → Provide appropriate aftercare and follow-up

Unresolved → Repeat at hourly intervals up to 4 cycles

OTHER INDICATIONS

Reconstitute Hyalase® in 5-10mls of solution (The ACE Group recommends dilution in 10mls bacteriostatic saline when only small amounts of filler are to be dissolved and 5ml dilution when treating Delayed Onset Nodules)

↓

Perform an intradermal test patch of 20 units of Hyalase® in the forearm and wait for 30 minutes

↓

No reaction/Minor erythema → Treat with Hyalase® – Be aware false negative patch tests do occur

Weal/Itching/Allergic reaction → Do not use Hyalase®

↓

Amount of Hyalase® to be injected depends on volume of filler to dissolve, concentration of hyaluronic acid, particle size and cross-linking. Amount injected should be titrated to clinical effect but a general guide is 5-30 units of Hyalase® per 0.1ml of hyaluronic acid.

↓

Use a suitable needle (smaller gauge size and length appropriate to depth, e.g. 4mm, 8mm, 13mm) and inject accurately and limited to the affected area covering the upper and lower borders of the product ensuring the product or nodule is injected directly. Several injections will be necessary to ensure complete dispersion and apply vigorous massage.

↓

Observe the patient for 60 minutes to ensure no reaction occurs.

↓

Review at 48 hours and consider further treatment if needed

↓

Consider antibiotic prophylaxis for inflammatory nodules.

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The ACE Group have produced a series of evidence based and peer reviewed guidelines to help practitioners prevent and manage complications that can occur in aesthetic practice. These guidelines are not intended to replace clinical judgement and it is important the practitioner makes the correct diagnosis and works within their scope of competency. Some complications may require prescription medicines to help in their management and if the practitioner is not familiar with the medication, the patient should be appropriately referred. Informing the patient's General Practitioner is considered good medical practice and patient consent should be sought. It may be appropriate to involve the General Practitioner or other Specialist for shared care management when the treating practitioner is not able or lacks experience to manage the complication themselves. Practitioners have a duty of care and are accountable to their professional bodies and must act honestly, ethically and professionally.

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