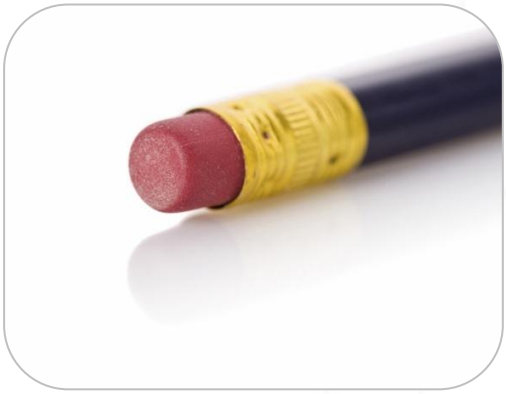
Feature Article

Hyaluronidase – A Magic Eraser?

"*Oops!*"... This is not a phrase any patient wants to hear their cosmetic practitioner say to them, but let's face it nobody is perfect and mistakes or unforeseen results do occur in all elective, cosmetic situations from time to time. The fewer the better we will all agree, which is why it's both important to learn how to avoid complications from the treatments that you perform, as well as how to effectively manage any which do, despite your best efforts, occur.



Thankfully in the case of hyaluronic acid based dermal filler products there is a solution which can be used to address and manage most complications which can occur with this type of filler material.

In this article we will discuss hyaluronic acid, some of the common complications associated with its application as a dermal filler product and how hyaluronidase can help to resolve issues.

What is Hyaluronic Acid?

You will see Hyaluronic Acid referred to by various words including Hyaluronan or Hyaluronate. The exact etymology breaks down that the word hyaluronic acid is derived from *hyalos* (the Greek for vitreous) and *uronic acid* because it was first isolated from the vitreous humour in the eye and possesses a high uronic acid content. The term Hyaluronate refers to the conjugate base of hyaluronic acid, i.e., the substance formed when an acid, in this case hyaluronic acid, loses a hydrogen ion. It is considered a base because it can gain a hydrogen ion to reform the acid. And because the molecule typically exists in vivo in its polyanionic form, it is most commonly referred to as hyaluronan. I think we'll just stick with HA for this article!

HA is a very important compound in the human body and is a naturally occurring polysaccharide found throughout connective, neural and epithelial tissues. It is one of the main components of the extracellular matrix and contributes to cell proliferation and migration. It is found in many tissues within the body, including the skin. The clever property of HA is its ability to bind 1,000 times it volume in water, much like a sponge. This makes it an ideal natural substance for retaining hydration and thus volume within the skin for example.

An average 70kg (11 Stone) person has approximately 15 grams of HA in their body at any given moment, with a third of it being degraded (enzymatically broken down and metabolised) and synthesized every day. It's estimated that 50% of that 15 grams is within our skin. As we age HA levels reduce, outwardly this shows in the appearance of our skin which can no longer hold the levels of moisture that it once did, thus plump, youthful pillow-like skin is lost. It is for this reason that many people turn to synthesised hyaluronic acids, injected into the skin via dermal filling and mesotherapy techniques as a method of increasing the HA levels and correcting discrepancies caused by ageing.

Because of its proliferation throughout the human body HA has been manufactured and developed over the years for a variety of medical and reparative indications. The first hyaluronan biomedical product, Healon, was developed in the 1970s for use in eye surgery.

However, through the process of development it was realised that natural hyaluronan molecules have a relatively short shelf life (approximately 24 hours) so different techniques of manufacturing have been tried in order to extend the length of the chain and stabilise the molecule for its use in medical and cosmetic applications, so that it lasts longer before degradation by the action of natural metabolism. Most synthesised HA is produced by bacterial fermentation from streptococci bacteria.

The introduction of cross-linking and stabilisation of the chains through chemical agents, such as those pioneered by the Q-Med NASHA® technology paved the way for longer lasting, more predictable products for cosmetic use. The technologies and manufacturing methods used in the last 20 years have meant that there are now a great variety of HA based fillers on the market, all touting different levels of unique attributes based on the way in which the original hyaluronan molecule has been 'shaped' into the packaged product; the levels of cross-linking, the agents used in the process (e.g., BDDE) and the recipes which can dictate how much cross-linked HA is mixed

with uncross-linked HA in the final product. All make for varying types of 'bread' in the HA bakery shop, in fact some would argue that the 'shop' is a little over saturated.

Depending on the composition and position of HA based dermal filler products, they can be expected to last between a few months and a few years before the product is metabolised by the body, as it would do with natural HA it had produced.

Complications

Apart from the normal side effects one would expect from an injectable treatment such as redness, swelling, bruising, pain or discomfort at the injection site for between 24-48 hours, treatment with HA dermal fillers (in the right hands) is generally considered to be a very safe and predictable procedure.

Because of its temporary nature, most complications or undesirable effects with HA based fillers are shortlived and will naturally resolve as the body metabolises the product over time. Although of course more serious complications can occur, mainly due to incorrect product placement and/or infection, necrosis, and in rare cases blindness have occurred.

More typical, and more minor complications such as nodule formation (granulomas), asymmetry, overfilling and a blue discolouration under the skin known as the Tyndall effect caused by injecting the product too superficially can be addressed by an experienced practitioner to the satisfaction of the patient using hyaluronidase.

What is Hyaluronidase?

Hyaluronidase, better known in the UK by the brand name, Hyalase® is a prescription only medicine from Wockhardt UK (formerly CP Pharmaceuticals) which is licensed for medical use. It is supplied as a 1500 I. U. white, freeze dried powder for solution for injection or infusion intramuscularly or subcutaneously in small ampoules (10 per pack). The powder should be dissolved in 1ml of water for injection immediately prior to use. The full SPC for Hyalase® is available **here**.

Hyaluronidase is a soluble protein enzyme that hydrolyses HA (causes chemical decomposition by reaction with water). It is more commonly used to speed up the dispersion and delivery of other drugs by lowering the viscosity of the hyaluronans in an area of the body to increase tissue permeability, for example when delivering local anaesthetics in ophthalmic surgeries. It also promotes the resorption of excess fluids and blood in tissue so can also assist in resolving oedema.

In the case of dermal fillers where extra HA has been added to the body, it can be used to target and hydrolyse this bolus of product, but depending on the amount used and the skill of application it can either simply correct the excess to a desired level (very difficult to do) or degrade the whole lot so you're back at square one. It's unlikely to start decomposing significant amounts of natural HA which it finds in the treated region particularly given that the body reproduces HA on a daily basis.

Resolution of HA fillers using hyaluronidase can be seen almost immediately or up to approximately 48 hours following application.

The use of hyaluronidase for this indication is off-label, however many clinicians will state that it is recommended as a necessary medication to have in a medical aesthetic clinic should the need to address HA dermal filler complications, asymmetries or overfilling arise. As a prescription only medicine this may not be possible for all business models, such as non-prescribing nurses operating as a sole trader providing dermal filler injections. In such cases, it is advisable to look into partnering with a prescribing practitioner so that you can offer this resolution to any patients who return with problems.

Risks

Contraindications to and severe adverse reactions from hyaluronidase are rare but some people do have a hypersensitivity to it and allergic reactions and anaphylaxis have been reported, particularly in those people who also have bee sting allergies. As with pre-treatment assessment, a full medical history before considering prescribing hyaluronidase is imperative.

Because of this risk it is considered advisable to perform a skin test on the individual before use of hyaluronidase. JL Cohen suggested in a 2008 clinical paper entitled **understanding, avoiding and managing dermal filler complications** (Dermatol Surg Jun;34, Suppl 1: S92-9) that 0.2ml of hyaluronidase should be injected intradermally into the patient and then they should be observed for 20 minutes. Should the patient demonstrate a

local wheal and flare reaction then a positive confirmation of hypersensitivity has been achieved and the patient should not be given hyaluronidase.

However, with the rarity of severe allergic reactions, it's up to the practitioner to evaluate the need for skin testing on all patients prior to hyaluronidase use, based on thorough medical histories and in-clinic provision to deal with any instance of anaphylaxis, such as on-site epinephrine.

Conclusions

Hyaluronidase, although important to have in your clinical setting, should not be seen as a crutch upon which to rely. It's not a *Magic Eraser* which allows one to be cavalier with one's approach to dermal filler treatments, such as by attempting new techniques or experimental product placement thinking that hyaluronidase will make everything better should it not work.

There's no substitute for training (initial and ongoing), as well as building knowledge of both the products which you use and their mechanisms of action within the skin, and the techniques and protocols which you use to deliver them.

If you find yourself needing to consider the use of hyaluronidase in a patient, these top tips from Dr. David Eccleston, Medical Director of MediZen Clinic in Birmingham are worth considering:

- **Dilution:** I add 1ml of saline to 1500 unit vial (of Hyalase), then withdraw 0.1ml and make that up to 1ml again, giving me a concentration of 15 units per 0.1ml. I then inject the same volume of Hyalase as the original volume of HA filler.

- **Application:** I have used it to correct lips, cheek overvolumising and even in one case Macrolane® nodules in the breast.

- **Technique:** I use a 1ml syringe with a 30g needle to inject it, using an ante grade tunnelling technique along the line of the filler or a serial puncture technique. Be careful under the eyes as there are superficial vessels there and stay below the orbital rim to avoid injuring the eye.

- **Massage:** I massage the product thoroughly to maximize spread through the problem area.

- **Safety:**

    - Hyalase should never be used without resuscitation facilities being available i.e. adrenaline, oxygen, etc.
    - It is being used off licence, and should only be injected by those trained in the technique and who can prescribe it.
    - It is not appropriate for non-prescribing nurses to administer in a salon or domestic setting.
    - Repeated injection, of what is an enzyme, is more likely to lead to sensitisation and potentially anaphylaxis so repeated use in the same patient is not advised.

And Dr. Eccleston's biggest tip of all? Get it right first time!

Useful Reading

Here is a list (not exhaustive) of some more recent clinical papers looking at the use of hyaluronidase in the resolution of HA filler complications.

Hyaluronidase in the correction of hyaluronic acid-based fillers: a review and a recommendation for use.
Rzany B, Becker-Wegerich P, Bachmann F, Erdmann R, Wollina U.
J Cosmet Dermatol. 2009 Dec;8(4):317-23.

Management of impending necrosis associated with soft tissue filler injections.
Dayan SH, Arkins JP, Mathison CC.
J Drugs Dermatol. 2011 Sep;10(9):1007-12.

Vascular complications of hyaluronic acid fillers and the role of hyaluronidase in management.
Kim DW, Yoon ES, Ji YH, Park SH, Lee BI, Dhong ES.
J Plast Reconstr Aesthet Surg. 2011 Dec;64(12):1590-5.

Low dose of Hyaluronidase to treat over correction by HA filler--a case report.
Menon H, Thomas M, D'silva J.
J Plast Reconstr Aesthet Surg. 2010 Apr;63(4):e416-7.

Treatment of injectable soft tissue filler complications.
Sclafani AP, Fagien S.
Dermatol Surg. 2009 Oct;35 Suppl 2:1672-80.

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Lorna has been Editor of The Consulting Room™, the UK's largest aesthetic information website, for nine years. She has become an industry commentator on a number of different areas related to the aesthetic industry, collating and evaluating statistics and writing feature articles, blogs, newsletters and reports for The Consulting Room™ and various consumer and trade publications, including *Aesthetic Medicine*, *Cosmetic News* and *Aesthetic Dentistry Today.*

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