

Hyaluronidase Pearls in Fillers Complications for the Practicing Physician

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ABSTRACT

BACKGROUND: With the growing use of hyaluronic acid fillers and the concerning sequelae of these products, hyaluronidase has become a must-have rescue treatment for such complications.

AIMS: The author aimed to present the collective knowledge existing in the medical literature in a manner that would be a practical guide to daily practicing physicians who utilize hyaluronic acid fillers in their clinic.

PATIENTS/METHODS: A review of the medical literature using the Pubmed search engine for articles on hyaluronidase, hyaluronic acid filler complications, and their management.

RESULTS: There is a plethora of papers addressing filler complications and their treatment approach. Most, if not all, address these complications and use of hyaluronidase in a specific indication, such as vascular occlusion, or addresses the topics in depth which

might not be suitable as a quick and practical guide to the day-to-day practicing aesthetic physician.

CONCLUSIONS: Utilizing the invaluable information existing in the medical literature to extrapolate the practical tips for using hyaluronidase to treat hyaluronic acid filler complications, the author compiled a practical guide for the practicing aesthetic physician to simplify their approach and to serve as a concise reference on this important topic.

Key words: Hyaluronidase, hyaluronic acid filler, complications

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INTRODUCTION

Hyaluronic acid fillers use in soft tissue augmentation is the second most common performed nonsurgical cosmetic procedure^[1]. With the existing possibility of complications secondary to these hyaluronic acid products, especially vascular occlusion, hyaluronidase is an essential product in the aesthetic physician's armamentarium nowadays.

TYPES OF HYALURONIDASE

There are different products of hyaluronidase, depending on its origin. Some are from human origin while some are derived from ovine or bovine testicular sources, and some types of hyaluronidase have unknown and non-specified origins. With that in mind, not all hyaluronidase products behave the same in the sense of reactivity and efficacy. It has been shown that ovine or human hyaluronidase are less allergic than bovine hyaluronidase, and the ovine product has a slightly greater activity against a different range of hyaluronic acid products^[2].

NOT ALL HYALURONIC ACIDS ARE EQUAL

As it has come to pass that hyaluronidase products have different efficacy on hyaluronic acid products, the same has been shown to be true

for the sensitivity of the different hyaluronic acid products to the hyaluronidase, it's been shown in studies that different hyaluronic acids respond differently and vary in susceptibility to the enzymatic degradation of the hyaluronidase and this may be contributed to the higher hyaluronic acid content, the degree of crosslinking, and the cohesive property of the gel filler as some hyaluronic acid gels required double the amount of other products to have a similar susceptibility to the hyaluronidase degradation Efficacy^[3-5].

HYALURONIDASE INTERACTION

Hyaluronidase immediately acts once in contact with the substrate, and its activity is typically of 24 to 48 hours duration in dermal tissue. However, it has an extended duration in ocular tissue that ranges from 60 to 112 hours. In contrast to that, the enzyme is deactivated immediately when injected intravenously^[3,5].

WHEN IS HYALURONIDASE USEFUL?

Indications that might face the practicing physician were hyaluronidase is particularly useful would be considered according to severity of the resulting complication. Some are considered nonemergency complications such as Tyndall effect were the product is placed superficially and reflects a blueish Hue color. Nodules and lumps or granulomas may also result as side effects from using hyaluronic acid fillers. An important noteworthy factor that if there is an active infection or it is at least suspected, hyaluronidase shouldn't not be used or injected until after initiating the appropriate antibiotic treatment otherwise the enzyme can facilitate spreading of the infection to the surrounding areas^[5,6].

Dosage for such indications varies widely in the literature, with average dosage can range from 15 to 75 units, though it has been generally suggested as a rule of thumb that for each 0.1 cc of hyaluronic acid to be a dissolved in vivo, the physician should start with five units of hyaluronidase for Restylane products and 10 units for Juvederm products.^{3,4} It's also worthwhile mentioning that when hyaluronidase is used to decrease the size of a lump or nodule that when 20 units of hyaluronidase was compared to 40 units, it did not show any statistical significance and both resulted in decrease of the palpation scale of the lumps^[7].

A more brilliant way for addressing minor fillers asymmetry, texture abnormalities and nodules ; and to be honest a more cost effective way; rather than dissolving all of the filler it can be corrected safely and effectively with low volume and low dose hyaluronidase that ranges between 1.5 to 9 units per 0.1 cc, of course this may be repeated weekly until the problem is resolved. Again, Juvederm compared to Restylane needed a greater dose of hyaluronidase to dissolve^[8].

But the approach is drastically different when dealing with the dreaded side effects of hyaluronic acid fillers, i.e. vascular occlusion. There are different approaches and algorithms for treating vascular occlusion secondary to fillers specifically when using hyaluronidase in the case of hyaluronic acid gels. The surface area involved and the time factor are of most important gauges when treating such side effects as the administration of hyaluronidase within four hours of the filler injection can significantly reduce the resulting necrosis of the tissue when compared to a more delayed injection of hyaluronidase after 24 hours the filler injection^[9]. In regard to the area involved and the spread of the damage one approach would be to give one injection every three to four centimetres of the ischemic area that is showing either blanching or violaceous reticulated discoloration followed by thorough massage and if there is no improvement within 60 min-

utes additional injection cycles are performed^[5]. But a more practical approach, in this author's opinion, would be using a high dose pulsed hyaluronidase approach with a suggested dosage of 500 units for each one vascular territory, not based on the hyaluronic acid amount that has been injected. The area afterwards should be massaged thoroughly to help with the increased contact of the hyaluronidase with the product and this is repeated hourly until signs of recovery and re perfusion of the skin and/or correction of blanching and the livedo signs^[10-12].

Of course it is important to mention that the hyaluronidase does not need to be actually injected intravascular to have an effect on the hyaluronic acid degradation, as when compared between intraarterial and subcutaneous hyaluronidase injection, the subcutaneous injection treatment actually showed better recovery of blood perfusion^[13,14].

The most fearful vascular occlusion event is that of the ophthalmic artery secondary to the forceful injection of the fillers through a distant branch that may cause the filler to travel in a retrograde direction through the proximal branches^[15,16]. According to the literature the most common injection locations that have been related with such an event are the glabella, nose, forehead, and the nasolabial folds amongst other^[17,18]. When this horrendous and frightening event does happen, treatment is needed urgently as the retina can only withstand up to 90 minutes of hypoxia before permanent damage starts to kick in. What is recommended that within that time frame at least 500 units should be delivered either in a retrobulbar injection or a peribulbar approach^[19]. No one can help but wonder are these therapeutic options even effective? well considering the risk and the gravity of loss of eyesight if nothing is done and the sparsity of other options available within such a small and tight time frame and despite the conflicting evidence in the literature, it is more likely to be beneficial but if only the hyaluronidase is administered as soon as possible^[20].

SIDE EFFECTS OF HYALURONIDASE

In general, side effects from hyaluronidase products are uncommon and fewer than 0.1% of patients who receive it have reported urticaria or angioedema. To test for such side effects three units of hyaluronidase are injected intradermally and if a local wheal and flare occurs within five minutes and persists 20-30 minutes it is considered a positive reaction, erythema alone does not constitute a positive reaction. Of course, in vascular occlusion events no pretests is performed as in such circumstances time is of the essence and in case an allergic reaction does occur, the availability of epinephrine is highly recommended^[5,6].

IS THERE LEGITIMATE CONCERN FOR THE NATIVE HYALURONIC ACID?

A valid concern worth mentioning is if the injected hyaluronidase has any effect on the native hyaluronic acid? It has been shown when hyaluronidase used at dosage of up to 375 units to dissolve a hyaluronic acid filler in one patient's face over a period of 10 days showed no concerning changes in the facial volume^[6], Though another publication showed that the endogenous hyaluronic acid does become diminished at dosage greater than 300 units^[2], It's been hypothesized that despite that, it is probably rapidly compensated by natural mechanism of hyaluronic acid synthesis^[7].

HYALURONIDASE PRECAUTIONS

Hyaluronidase should be used with caution if the patient is receiving frusemide, epinephrine, benzodiazepines, heparin, and phenytoin as

these have been found to be incompatible with it. Where salicylates, cortisone, estrogens, adrenocorticotrophic hormone, and antihistamines appeared to render tissues partly resistant to the enzymatic action of hyaluronidase. Ocular malignancy is considered a contraindication for hyaluronidase as it might facilitate the spread of the malignant cells to the surrounding areas. Hyaluronidase is pregnancy category C^[6].

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