Treatment of Hyaluronic Acid Filler–Induced Impending Necrosis With Hyaluronidase: Consensus Recommendations

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Abstract
Injection-induced necrosis is a rare but dreaded consequence of soft tissue augmentation with filler agents. It usually occurs as a result of injection of filler directly into an artery, but can also result from compression or injury. We provide recommendations on the use of hyaluronidase when vascular compromise is suspected. Consensus recommendations were developed by thorough discussion and debate amongst the authors at a roundtable meeting on Wednesday June 18, 2014 in Las Vegas, NV as well as significant ongoing written and verbal communications amongst the authors in the months prior to journal submission. All authors are experienced tertiary care providers. A prompt diagnosis and immediate treatment with high doses of hyaluronidase (at least 200 U) are critically important. It is not felt necessary to do a skin test in cases of impending necrosis. Some experts recommend dilution with saline to increase dispersion or lidocaine to aid vasodilation. Additional hyaluronidase should be injected if improvement is not seen within 60 minutes. A warm compress also aids vasodilation, and massage has been shown to help. Some experts advocate the use of nitroglycerin paste, although this area is controversial. Introducing an oral aspirin regimen should help prevent further clot formation due to vascular compromise. In our experience, patients who are diagnosed promptly and treated within 24 hours will usually have the best outcomes.

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Vascular compromise after soft tissue augmentation with filler substances is a major concern, as either frank intravascular injection or, less commonly, arterial compression can prevent blood flow through arteries supplying the skin or even the eye.1–4 Certain regions of the face, such as the glabella, are at a higher risk for developing compromised blood flow and necrosis given their vascular anatomy, although there have been reports of tissue necrosis at the nasal ala, lip, and nasolabial fold areas following treatment with hyaluronic acid (HA) or calcium hydroxlapatite (Figure 1).1,2,5–7 Impending necrosis has been reported in cases involving all types of filler materials (including collagen and HA), with incidences estimated at 0.001% of total procedures performed.5,8

MANAGEMENT OF IMPENDING NECROSIS
Injection-induced necrosis is a rare but dreaded complication associated with the use of soft tissue augmentation filler...
agents. Necrosis can occur from interruption of the vascular supply to the area, potentially by compression or injury, but usually from obstruction of the vessel(s) through injection directly into an artery, causing an embolism that impedes blood supply. In order to avoid serious, potentially irreversible complications, all physicians should have a heightened awareness of the possibility of vascular compromise when using fillers, specifically look for a regional blanch, and have an established treatment algorithm in place if a blanch is suspected or overtly occurs. In these circumstances, patients often report symptoms of necrosis varying from extreme pain with geographic discoloration (such as a violaceous hue) to a dull persistent ache.

Hyaluronidases are soluble protein enzymes that degrade HA and are used to increase drug diffusion and reverse the effects of HA fillers. Their role in treating complications from HA fillers has recently been reviewed. Commercial formulations include Vitrase (purified ovine testicular hyaluronidase) and Hylenex (purified recombinant human hyaluronidase). Hyaluronidases should be accessible in any office that routinely performs soft tissue augmentation with HA fillers.

We provide a systematic protocol for its reconstitution below based on literature review and personal experience, including the possible need for skin testing and application in the management of impending necrosis. In addition, a clinical example of impending necrosis is shown in Figure 2 and an outline of a suggested treatment algorithm in Table 1.

**TREATMENT PROTOCOL AND EXPERT RECOMMENDATIONS**

1. Use a significant amount of a hyaluronidase enzyme in the area of necrosis (i.e., Vitrase at 200 U).
   
   It is important to avoid under-treatment when dealing with necrosis, as this could have very significant consequences in the regional cutaneous tissue, such as scabbing and significant scarring. With some HA products [such as Restylane and Perlane (Galderma Laboratories, LP, Fort Worth, TX)] it may be possible to use smaller volumes of a hyaluronidase to dissolve the HA compared to that required for products such as JuveDerm (Allergan, Inc. Irvine, CA). But necrosis is an urgent situation and it is most important to flood the area with a sufficient hyaluronidase enzyme to try to break up or dissolve some of the product as quickly as possible. In animal experiments, early injection of a hyaluronidase (4 hours after HA filler injection into the auricular arteries of the rabbit) reduced the size of necrotic areas compared to delayed injection of a hyaluronidase (24 hours after filler injections) or untreated controls.

   We recommend the immediate use of a minimum of 200 U of Vitrase in all cases of impending necrosis.

   Although a hypersensitivity reaction can occur rarely with a hyaluronidase (published incidence of 1 in 1000 patients)—it is not felt necessary to conduct a skin test in cases of impending necrosis. However, the treating physician should be prepared for the rare possibility of allergy and even the extreme possibility of anaphylaxis. Skin testing with a hyaluronidase is rarely performed by our expert panel when dissolving the non-urgent circumstance of undesired bumps or nodules of HA.

   Some experts prefer to dilute a hyaluronidase with lidocaine in order to facilitate vasodilation and dispersion when trying to treat someone who has impending necrosis. An alternative would be to dilute the hyaluronidase with saline to allow for more volume and thus cover a larger area per 200 units of a hyaluronidase, but clearly saline would not have the potential vasodilatory properties of lidocaine on local vessels.

   A hyaluronidase should be injected into the area where the circulation of blood supply appears to be reduced (i.e., the area of blanch or violaceous discoloration). There is no need to inject more than a few sites in

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**Figure 1.** Cross-section of the central third of the lower lip of a female cadaver (age unknown), showing the cross-sectional anatomy of the orbicularis oris muscle and the location of the labial artery. The labial artery is located posterior to the wet dry line, deep to the labial mucosa, but superficial to the orbicularis oris muscle. The arrow points to the labial artery, adjacent to the orbicularis oris muscle. This region is often injected in techniques designed to increase lip eversion (posterior or deep to the labial artery region) or techniques designed to increase lip fullness (anterior and superior to the location of the labial artery region in the figure). Because of the proximity of the labial artery to the field of injection, this region may be considered to be a higher risk area to treat with injections of dermal filler.
the area of impending necrosis unless it is a large area or region, since the material diffuses readily through fascial planes and can be massaged through the treatment area. Our expert panel feels that one injection for every 3-4 cm of skin manifesting signs of necrosis is appropriate.

If no improvement (such as less blanching and a less dusky, violaceous color) is seen within 60 minutes, additional quantities of a hyaluronidase should be injected (repeating 3-4 cycles).

A prompt diagnosis and immediate treatment with high doses of a hyaluronidase are critical to success.

(2) Upon first recognition of vascular compromise (such as a regional blanch of the skin in a distribution reflective of the underlying vasculature), apply a warm compress and massage vigorously.

The warm compress promotes vascular dilation\(^9,23\) and massaging\(^8\) at the site may help to break a focal obstruction. Apply a warm compress for 5-10 minutes every 30–60 minutes (avoid burning the skin). Patients may or may not report the onset of immediate pain, or sometimes recount “normal” injection-related discomfort failing to resolve. In many circumstances, a reticulated and violaceous dusky pattern may be seen within a few hours or by the next day. Thus, an immediate blanching and/or a delayed reticulated pattern of the injected area are important clinical observations. A hyaluronidase, in significant quantities (see below), should be used immediately upon suspicion of vascular compromise, regardless of whether this is noted straight away or in a delayed time frame.

(3) Massage topical nitroglycerin (NTG) paste into the area.

Because of its vasodilatory properties, topical NTG may reduce necrotic spread.\(^4,24\) However, the use of NTG paste when dealing with necrosis is controversial. The amount of NTG recommended is dependent on the size and area of impending or full necrosis. We recommend application of NTG paste immediately on suspicion of necrosis and up to 2-3 times daily, provided that the patient is not debilitated with severe headaches or light-headedness from the NTG itself. Care should be

Figure 2. This 55-year-old woman presented 4 hours after a hyaluronic acid injection into the lower lip at an outside clinic. (A) On the first injection the lips were seen to blanch and then became mottled. Hyaluronidase (400 U) was injected into the lower lip and a warm compress was applied. No further treatment was undertaken and improvement can be seen (B) after 1 day and (C) a few days later.
(4) Introduce an oral aspirin regimen.

Start the patient on an oral aspirin regimen of 2 pills of 325 mg daily to try to prevent further clot formation due to vascular compromise, and an antacid to prevent aspirin-associated gastritis. The duration of aspirin treatment would depend on the clinical scenario and whether improvement is seen, but in our experience a 1-week course would be typical.

(5) Follow patients daily for signs of improvement or any further signs of occlusion or necrosis.

A hyaluronidase and NTG can be continued as needed over the next few days. It is important that patients are followed daily at this critical stage.

(a) If improvement is noted the NTG paste massages can be stopped, although there is some anecdotal evidence that continued use of NTG for 1–2 days, if tolerated, can accelerate resolution of the reticulated vascular congestion.

(b) If there is no improvement or if progression of necrosis occurs the above regimen of a hyaluronidase, NTG paste, and aspirin should be repeated daily, typically for 2-3 days.

(6) Other considerations:

(a) It has been suggested that hyperbaric oxygen could be used in instances of severe necrosis or delayed presentations in which the tissue is not healing well. Hyperbaric oxygen has the potential to deliver oxygen deep into the skin and may help to keep oxygen-dependent tissues viable. It is frequently used for wound healing in compromised vascularity. Intuitively it makes sense, but with so many variables involved and experience limited, it is hard to assess its true value fully.

(b) It has been postulated that topical oxygen “cosmeceutical therapy” to the affected area twice daily could potentially enhance the rate of epithelialization. However, data to support this practice are weak and completely anecdotal.

(c) There have been recommendations for other products, such as low molecular weight heparin use, intravenous prostaglandin E, and also Sildenafil (Viagra) in the armamentarium, to try to treat impending necrosis.

(7) Patient aftercare involves routine wound care, ensuring adequate hydration, frequent appropriate wound debridement of necrotic skin, general supportive care, and monitoring for secondary infection.

Minimize scarring by providing diligent wound care with daily dressings, depending on the location, depth of wound, and amount of tissue loss. Keep the wound covered with ointment to prevent crusting and minimize bacterial contamination until healing is complete. Peroxide can potentially impede wound healing and is not recommended. Patients who are diagnosed promptly and treated within 24 hours will usually have the best outcomes. A delay in diagnosis and treatment has been associated with some degree of skin loss, ulceration, and delayed healing, requiring many weeks of wound care, and can result in different degrees of scarring.

**DISCUSSION**

Injection-induced necrosis is a rare but serious consequence of soft tissue augmentation with filler agents. The use of hyaluronidases to prevent serious, potentially irreversible complications is “off label” and published data are limited. Our collective experience has demonstrated that a prompt diagnosis and immediate treatment with a hyaluronidase is both effective and essential. For the first time we can provide a systematic protocol for the use of hyaluronidases, along with other measures or adjunctive treatments that can help, such as aspirin.

While our priority is to instruct in the prompt diagnosis of impending necrosis and its immediate treatment with high doses of a hyaluronidase (at least 200 U), the benefits of dilution, use of cannulas, and use of NTG paste are still debated.
Cannulas, for example, would appear to be safer; however, their use must be balanced against control of the injection.

It is important to recognize that doses that have been observed to be effective against one product will not necessarily apply to other formulations. Thus, the recommendations in this consensus document apply to the most widely-used hyaluronidase product (Vitrase), where we have the most experience. Specific knowledge of the hyaluronidase used can help determine the initial dose required for treatment of adverse events.

CONCLUSION

A prompt diagnosis and immediate treatment of impending necrosis with high doses of a hyaluronidase (at least 200 U) are critically important. It is hoped that the recommendations we provide are helpful and will encourage further clinical investigation.

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