

# Extensive necrosis after injection of hyaluronic acid filler: case report and review of the literature

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## Summary

**Background** Use of dermal fillers for soft tissue augmentation has become an integral part of aesthetic practices. Dermal fillers temporarily remove the appearance of rhytids and reduce the depth of skin folds. Even with the most experienced of injectors, adverse effects can and do occur ranging from mild bruising to severe injection necrosis.

**Aims** Physicians should be able to treat the severe complication of vascular necrosis and detect impending necrosis after injection of a dermal filler, especially with hyaluronic acid fillers.

**Materials and Methods** Case report of a patient who was followed for 6 months from time of injection of hyaluronic acid filler to complete healing of wound.

**Results** Complete wound healing was achieved with early recognition and institution of treatment.

**Discussion** We review a case report of injection necrosis and methods used to prevent and treat this complication.

**Conclusion** Early recognition of vascular necrosis with specific protocol for treatment after injection necrosis with hyaluronic acid fillers improves the outcome of wound healing.

**Keywords:** face, hyaluronic acid, necrosis, vaso-occlusion

## Introduction

Injectable fillers have become a large part of esthetic practice over the last 25 years. Bovine collagen was introduced in the 1970s as the first Food and Drug Administration (FDA) approved injectable filler. Hyaluronic acid (HA) was FDA approved in the US in January 2004 as a dermal filler for correction of wrinkles and skin folds.<sup>1</sup> In 2007, the administration of botulinum toxin was the top nonsurgical procedure in the

United States, followed by injections of HA-based dermal fillers, according to the American Society for Aesthetic Plastic Surgery.<sup>2</sup> Over 1.5 million soft tissue filler procedures were performed in the United States in 2007 with HA being the most frequently used agent.<sup>3</sup>

Hyaluronic acid is a natural complex sugar that retains water; it is found throughout all living organisms. It is a linear polysaccharide chain consisting of regular repeating sequences of monosaccharides D-glucuronic acid and N-acetyl-D-glucosamine and is a naturally occurring component of the dermal extracellular matrix, connective tissue, and vitreous humor of the eye.<sup>1,4</sup> HA absorbs more than 1000 times its weight in water and adds volume to the skin's surface. HA also binds with collagen and elastin and transports essential

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nutrients to these fibers. The triple combination of collagen, elastin, and HA provides structure, elasticity, and volume to the skin and contributes to its overall appearance.<sup>5</sup>

As such, physicians use HA to restore durability of skin, because HAs provide for effective soft tissue augmentation in the comprehensive approach to non-surgical facial rejuvenation. Its anti-aging effects are apparent as an increase in skin volume and a smooth, natural appearance. Soon after it was introduced several years ago, it became the standard for filling wrinkles around the eyes and mouth and augmenting lips.

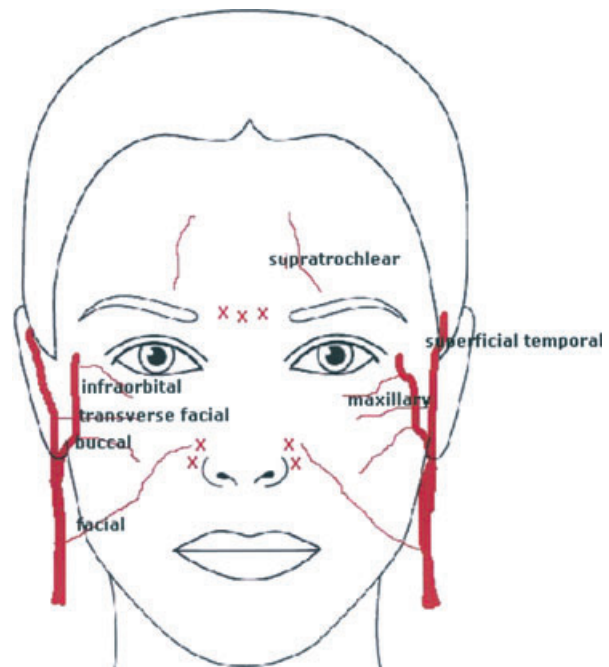
We are reporting a case of a 52-year-old man who had extensive necrosis in the right cheek after injection of a HA dermal filler.

### Case presentation

A 52-year-old man was treated in March 2010 for injection of a dermal filler. The injection with HA (Perlane®; Medicis Aesthetics) was performed by an experienced plastic surgeon and given percutaneous into the right cheek in and around an atrophic acne scar. The scar was deep, pitted, well demarcated, rolling, boxcar, nonpigmented, and nonerythematous, with no overlying papules or pustules on his right cheek. The patient had many injections with calcium hydroxyapatite (CaHA; Radiesse®; Merz Aesthetics, Frankfurt, Germany) for the scar in the past; the last one was 6–7 months prior to this injection.

The patient was injected with 2 cc of HA in the deep dermis and subcutis; he had bluish discoloration and pain in the first several hours but attributed it to “normal bruising.” Because of persistent pain, he returned to the clinic 5 days later.

Physical examination revealed well-demarcated areas of slough, necrosis, and poor capillary refill in the central portion of the ipsilateral cheek extending into the nasolabial and ophthalmic areas (See Fig. 1). Extensive necrosis occurred in the area of the cheek supplied by the facial artery, transverse facial artery, the buccal



**Figure 2** Vessels nurturing the cheek area; facial artery, transverse facial artery, the buccal branch of the maxillary artery, the infraorbital, and the zygomatic branch of the lacrimal artery. Danger zones for injection of dermal filler. Note potential complication of vascular necrosis after injection. The supratrochlear vessels are involved in necrosis at the glabellar region. The dorsal nasal artery is involved in necrosis of the nasal alar region.



**Figure 1** Day five postinjection. Note sloughing, superficial infection, and early eschar formation.



**Figure 3** Day six postinjection. Note decreased sloughing and continued healing.



**Figure 4** Three weeks postinjection. Note significant improvement in healing.

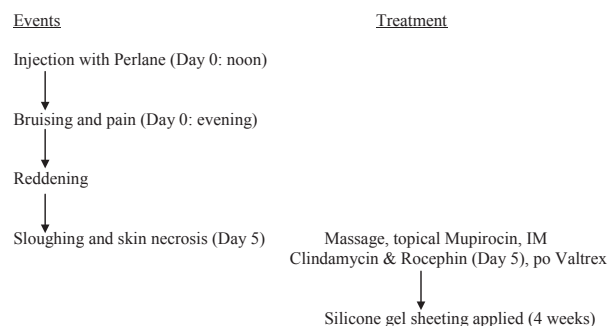


**Figure 5** Four weeks postinjection. Note significant improvement in healing.

branch of the maxillary artery, the infraorbital, and the zygomatic branch of the lacrimal artery (See Fig. 2). The facial vein may have also been compressed or occluded at the time of injection.

Immediately upon arrival, under care of the surgeon, mupirocin was applied topically, one IM injection of clindamycin, and one IM injection of ceftriaxone was given. He was also treated empirically with valacyclovir 1 g bid  $\times$  5 days without culturing because of time delay for results of culture. Hyaluronidase is an established treatment for vascular compromise after injection with HA but was not used in our case because of delayed presentation.

Improvement was noticed the following day (day 6 after injection) with erythema, and a line of demarcation was seen (See Fig. 3). He was then started on oral antibiotics with amoxicillin/clavulanate for 1 week. At 3 weeks, there was a significant amount of healing



**Figure 6** Flow chart describing timing of events and treatment given.



**Figure 7** Four and a half weeks postinjection. Note eschar sloughed off.



**Figure 8** Five and a half months postinjection. Note healing with scar formation.

(See Fig. 4). At 4-week postinjection, silicone gel sheeting was applied to the wound and mupirocin was discontinued (See Fig. 5). By 3½ months, the wound had

completely healed. The patient was then seen on an outpatient basis monthly when wound healing was assessed. At-home care consisted of sun avoidance, application of silicone gel sheeting with instructions to keep the area dry. See Figure 6 for timing of events and management. Figures 7 and 8 show healing at 4½ weeks and 5½ months postinjection, respectively.

## Discussion

Hyaluronic acid was discovered in 1934 by Karl Meyer and John Palmer, scientists at Columbia University, New York.<sup>5</sup> They isolated the substance from a cow's eye and conceived the name from hyalos (Greek work for glass) and the uronic sugar found in the substance.<sup>5</sup> Over the next 50 years, Endre Balazs made the majority of discoveries relating to HA, including esthetic uses such as tissue augmentation.<sup>5</sup>

Perlane® (HA; Medicis Aesthetics) is one form of HA, an FDA-approved nonanimal-stabilized hyaluronic acid (NASHA) derivative used for soft tissue augmentation. It is derived from fermentation of *Streptococcus equi*, chemically crosslinked with butanediol diglycidyl ether, stabilized, and suspended in phosphate-buffered saline at pH 7 and a concentration of 20 mg/mL; prepared as 940–1090 µm gel particles.<sup>3</sup>

Adverse effects after injection of an HA dermal filler that are common include temporary redness, discomfort with injections (therefore local anesthesia is used), firmness, swelling, and bruising. Papules and nodules, migration of product, itching, discoloration, and allergic reactions are uncommon. Injection necrosis is a rare complication.<sup>6</sup>

Injection necrosis can be attributed to an interruption of vascular supply because of compression or frank obstruction of vessels by direct injection of the material into a vessel itself. In the case described earlier, 2 cc of Perlane® (HA; Medicis Aesthetics) was given in and around a scar that had been filled multiple times before. Skin necrosis is believed to have been caused by injection of a large volume of filler into a tight space at the scar area, resulting in compression and subsequent occlusion of a vessel. Since the last injection of CaHA was given 6–7 months prior, the presence of persistent CaHA could likely increase the chances of necrosis with the HA injection. Venous occlusion occurs if excessive amounts of fillers are placed in a small area, leading to excessive venous congestion. This is associated with persistent dull, aching pain, and swelling, with the development of a violaceous discoloration of the affected area; these findings can easily be misinterpreted and dismissed as early discomfort and bruising after treatment, but a

violaceous reticulated patch is present with vascular compression/occlusion, and pain out of proportion (in terms of severity or persistence) to the treatment or for the individual patient should be further investigated.

In a German Injectable filler study (2003–2008), of 10 patients treated in the glabellar region with HA, vascular complications occurred in two of the patients (20%).<sup>6</sup> Inoue *et al.*<sup>7</sup> report on a vascular reaction to a HA product in the ala of the nose in a female patient. Results showed that occlusion of the dorsal nasal artery may cause compromise of skin at the alar region. Schanz *et al.*<sup>8</sup> report a vascular complication in a 35-year-old man after HA injection in the glabellar region. The supratrochlear vessels are thought to be involved in glabellar necrosis. Inoue *et al.*<sup>7</sup> reported a case of skin necrosis after HA gel was injected to shape the nasal tip contour. Immediately after injection, the patient had a striking pain on the left side of her face. A few hours later, she noticed reddish discoloration.<sup>7</sup> The 6th day, a gangrenous skin necrosis was present on the left nasal ala.<sup>7</sup> Computed Tomography (CT) angiography on the 9th day demonstrated local occlusion of the angular branch of the facial artery and compensatory dilation of collateral vessels such as the infraorbital artery and its daughter branches.<sup>7</sup> A biopsy specimen from the nasal ala indicated intra-arterial and subdermal deposition of foreign bodies.<sup>9</sup>

Hirsch *et al.*<sup>10</sup> described a 44-year-old woman who developed patchy erythema and violaceous reticulated foci in the area of the nasolabial folds where HA was injected. Because of the occurrence of events beginning 6 h after injection, embolization of the angular artery was suspected rather than compression of the vessel from the filler, which typically presents immediately after injection. Immediate discontinuation of injections, gentle massage, two 325 mg enteric-coated aspirin, topical nitroglycerin paste, and hot compresses were applied to the area, and 30 U of hyaluronidase was injected into the deep dermal and subcutaneous layer of skin along the distribution of the angular artery and superior labial artery. Eight hours later, improvement was reported with no signs of necrosis, and normal exam at 2-week follow-up.<sup>10</sup>

Hirsch *et al.*<sup>11</sup> also reported a patient with a similar clinical presentation after injection of an HA filler into the nasolabial folds, only symptoms began at 48 h after injection instead of 6 h. In this case, 325 mg aspirin, topical nitroglycerin paste, and hot compresses showed no improvement and continued worsening of pain. Because of the delayed presentation, the authors suspected a compressive event because of the presence of HA in addition to subsequent postinjection swelling



putting pressure on the small terminal branches of the angular artery. Because of lack of improvement, 30 U of hyaluronidase was injected along the course of the facial artery to diminish the volume of HA compressing the vessel. Follow-ups revealed significant improvement in pain and color with no adverse sequelae. The improvement with hyaluronidase suggested an additional mechanism of vascular compromise, possibly from the formation of a small embolus, because of inadvertent intra-arterial injection of HA.<sup>11</sup>

Cox<sup>12</sup> reported a case where multiple subcutaneous nodules formed after poly-L-lactic acid mixed with 2 mL 2% lidocaine, and 3 mL sterile water was injected in the face for volume replacement. This was said to occur with too superficial placement of the filler or with a low-volume dilution. Avoidance of the periocular area and a dilution of 8 mL were recommended. There was no improvement with steroid injections, and the nodules were surgically removed 18 months later. The Tyndall effect, bluish discoloration because of a filler being placed too superficially, is another complication and can be treated with 10–30 U hyaluronidase, with resolution in a few days.<sup>12</sup> Erythema and swelling 2–3 weeks after injection of HA filler can be because of infection and treatment with a 6 week course of minocycline and clarithromycin can resolve this complication.<sup>12</sup>

Another rare but extremely hazardous complication is reported by Silva and Curi<sup>13</sup> after injection of microspheres of polymethyl-methacrylate into the glabellar area. Blindness and total ophthalmoplegia occurred and was postulated to be because of filler being inadvertently injected into the supratrochlear artery, which travelled retrograde into the main trunk of the ophthalmic artery and then propelled forward by forceful injection to occlude other distal branches of the ophthalmic artery.<sup>13</sup>

In 2005, Brody<sup>1</sup> described a 68-year-old woman who presented with multiple warm, red, indurated nodules on the chin after she had HA injections. Biopsy was consistent with granulomatous foreign-body reaction to the HA or to the protein contaminants in the preparation. Several treatments were tried with little improvement; 3 mg/mL triamcinolone acetonide, antibiotics of cephalexin and trimethoprim-sulfisoxazole, multiple rapidly tapering weekly courses of prednisone, topical desoximetasone cream 0.25%, and tacrolimus ointment. These nodules were dissolved within 24 h using hyaluronidase. Brody<sup>1</sup> described another case where treatment with hyaluronidase was successful for dissolution of soft masses that formed under each eye after NASHA injections into the periorbital area.

Cohen and Brown<sup>14</sup> described anatomic considerations in minimizing the risk of necrosis in the glabellar

region. The supratrochlear artery exits the medial orbit and courses upward, supplying blood to the nasal root and the inferior central forehead. To avoid compression or injecting into the vessel, pinching the injection site helps to raise the injection area above the plane of the small, arborized branches of the supratrochlear artery.<sup>14</sup> Also, a volume of 0.2–0.5 cc is recommended to replace volume loss in the glabellar region, and avoidance of bulkier products and products that expand during rehydration (i.e., heavier HA fillers).<sup>14</sup>

For injection in the nasolabial folds, the coming together of embryonic fusion planes at the alar groove may not allow for the accommodation of filler volume and tissue distension.<sup>14</sup> The angular artery anastomoses with the dorsal nasal artery at the medial canthus and therefore has potential for intracerebral embolization.<sup>14</sup> The facial artery runs in an oblique direction over the mandible, crosses the nasolabial fold, runs toward the nasal side wall, and along the lateral nasal wall where it becomes the angular artery.<sup>15</sup> The lateral nasal artery branches from the facial artery at the junction of the facial artery and angular artery and supplies the nasal tip and ala.<sup>15</sup> This could explain alar necrosis after injection with a filler into the nasolabial fold or nasal tip, the first report described by Inoue *et al.*<sup>7</sup> after injection with Restylane (Q-Med, Uppsala, Sweden) into the nasal tip.

Schanz *et al.*<sup>8</sup> reported a case of a 35-year-old man who had been treated with 0.7 mL Restylane® (Medicis Aesthetics) in the glabellar region. The patient developed a violet and blue reticular pattern in the glabellar area, the bridge of the nose, and the left side of the nose without pain or discomfort and within minutes. Low molecular weight heparin (Fragmin P forte 5000 IE; Pharmacia, Peapack, NJ, USA) was given daily for a week when the reticular pattern began to fade.<sup>8</sup> An ulcer developed after 10 days and healed after 5 weeks with no residual defects. In this case, the dorsal nasal artery was affected and may have been because of the injection pressure perforating the vascular wall.<sup>8</sup>

## Treatment

Modalities of treatment used for vascular necrosis because of injection of HA fillers include: injection of hyaluronidase along the distribution of the underlying vessel, application of warm gauze for impending necrosis, and application of 2% nitroglycerin paste.<sup>6,9,16</sup> These procedures dissolve the product, promote vasodilation, and facilitate blood flow.

Hyaluronic acid has the advantage that it is the only filler that can be reversed with a simple injection. Hyaluronidase has been used in the management of the

soft tissue filler complication injection necrosis. It acts by hydrolyzing HA by splitting glucosaminidic bond between C1 of the glucosamine moiety and C4 of glucuronic acid.<sup>1</sup> Vitrase® (Ista Pharmaceuticals, Irvine, CA, USA), (used in our study), is a commercial product, derived from purified ovine testicular hyaluronidase, is preservative free, and contains lactose.<sup>4</sup> Skin testing for hypersensitivity, which is performed with 0.02 mL (3 U) of 150 U/mL solution placed intradermally, is recommended because of potential local site reactions, urticaria and angioedema, and the rare occurrence of anaphylactic-like reactions after retro-bulbar block.<sup>4</sup> Positive reaction for skin testing is a wheal appearing within 5 min and lasting for 20–30 min with localized itching.<sup>4</sup> It is contraindicated in inflammation, and insect bites to avoid spread of local infection and in those with allergy to bee stings.<sup>1,4</sup> Subcutaneous injection of hyaluronidase works immediately and lasts for 24–48 h.<sup>4</sup> Reconstitution of the dermal barrier removed by intradermal injection of hyaluronidase is complete in 48 h.<sup>1</sup>

In cases of severe or unresponsive necrosis, deep subcutaneous injections of low molecular weight heparin into the affected area has been recommended to promote vasodilation.<sup>16</sup> Once necrosis has occurred, wound debridement and diligent wound care with daily dressings on the debrided area minimize scarring.<sup>6</sup> A minimal of 3 months before surgical attempts at scar revision should be allowed for scar maturation and establishment of collateral circulation.<sup>6</sup>

Arterial occlusion is an immediate (0–2) days complication recognized clinically by blanching and severe pain. Treatment is as above with the addition of antibiotics.<sup>9</sup> Venous occlusion is a delayed complication (>14 days) appearing as dull pain and dark discoloration. Additional treatment includes antibiotics and consideration of hyperbaric oxygen in cases of impending massive skin necrosis.<sup>9</sup>

Inoue *et al.*<sup>7</sup> reported a patient that was treated with Intravenous (IV) alprostadil (Prostaglandin E-1; 120 µg/day) after which erythema improved. A full thickness skin graft taken from the postauricular area was grafted to the residual skin defect on the day 43 was successfully accepted.<sup>7</sup>

Tissue necrosis has been reported most as a complication of soft tissue augmentation in the glabellar region.<sup>17</sup> This is because of occlusion of the minute vessels branching from the supratrochlear and supraorbital arteries supplying the glabella – a watershed region with limited collateral blood flow.<sup>17</sup> Glaich *et al.*<sup>17</sup> reported a series of measures that help prevent or heal necrosis after injecting into the glabellar region. Preventive measures include: aspirate before injecting, inject superficially and

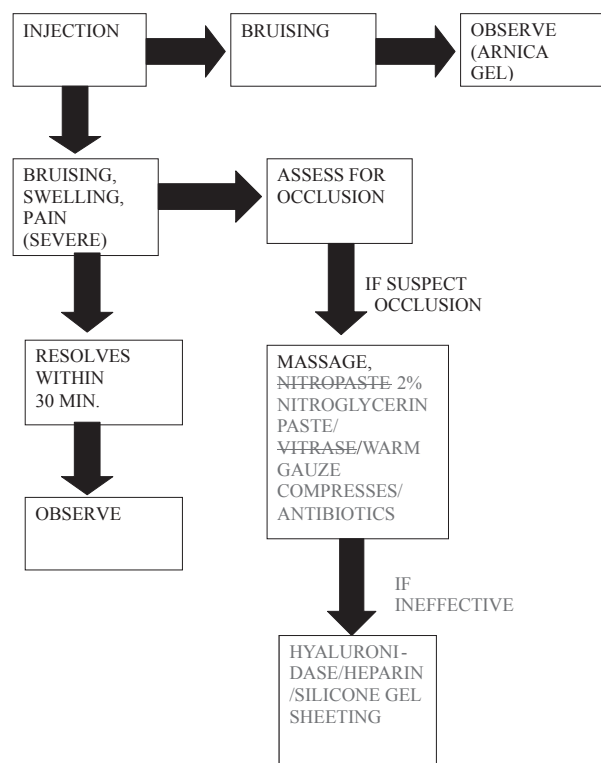
medially, and avoid overcorrection by using low volumes in two or more treatment sessions (rather than one high-volume session).<sup>17</sup> Treatment measures include, in addition to those aforementioned to promote vasodilation: application of nitroglycerin paste ½ inch to 1 inch of ointment with an applicator covering 3 cm of the surrounding area, leaving on for 12 h and off for 12 h until clinical improvement, 75 U hyaluronidase mixed with 1.5 cc lidocaine with epinephrine into areas of HA filler excess after skin prick testing, and low molecular weight heparin (Fragmin; Pharmacia) 5000 IU/0.2 mL daily deep subcutaneous injections to prevent thrombosis and embolization.<sup>17</sup> Care of the eschar involves soaking well in normal saline, keeping it moist with ointment (petrolatum or Aquaphore®; Belersdorf, Wilton, CT, USA) and occlude with Saran wrap.<sup>17</sup> Treatment of the resulting scar involves silicone pads and intralesional steroid injection.<sup>17</sup>

Hyperbaric oxygen therapy (HBOT) is US FDA approved for necrotizing soft tissue infections and chronic, nonhealing wounds.<sup>18</sup> Efficacy is shown for chronic wounds by increasing proliferation of fibroblasts and endothelial cells, differentiation of keratinocytes and keratinocyte migration, and increasing VEGF levels in the wound, thereby aiding granulation tissue and wound contraction.<sup>19–24</sup> HBOT is defined as the administration of 100% oxygen at a pressure of >1 atm.<sup>25</sup> HBOT promotes wound healing through cellular proliferation and angiogenesis and is performed at 2–2.4 atmospheres absolute (AMA) for a total of 90 min of 100% oxygen breathing time.<sup>26</sup> Treatment is performed daily for a minimum of 30 treatments, with extended courses based on the response to therapy.<sup>26</sup>

## Prevention

Preventative measures include having the patient stay for several minutes after the injection to observe for blanching. Injecting lidocaine without epinephrine can distinguish blanching because of vaso-occlusion from blanching because of epinephrine. Alternatively, a direct infiltration of 1% lidocaine with 1:100 000 epinephrine along the nasolabial folds will theoretically constrict the blood vessels and decrease the risk of piercing a blood vessel and causing ecchymosis or inadvertent injection of the substance into the vessel.<sup>27</sup> In our practice, the injectable fillers we use are mixed with lidocaine without epinephrine.

It is important to avoid areas with potential risk of vascular embolization; nasal ala,<sup>7</sup> or to take great caution when injecting specific areas; glabellar, nasolabial folds. (See Fig. 2). Also, overcorrection should be avoided,



**Figure 9** Prevention and treatment plan for vascular necrosis after injection of dermal filler.

aspirating before injecting and using low volumes of product in two or more treatment sessions instead of using a high volume in one session lowers the risk of vascular occlusion.<sup>16</sup> Additional measures include injecting with the smallest possible needle (30–32 gauge needles), injecting material with withdrawal, and proper plane of injection.<sup>9</sup> A thorough history with blood thinners, allergies, and scarring (keloids) should be taken. As a precautionary measure, in our clinic, we have added to our patients' postop instructions to observe for specific signs of impending necrosis.

## Conclusion

In recognizing the complication of vascular necrosis, one must be aware of pain and blanching that is not commensurate with treatment. Also, bruising from occlusion of a vessel will be associated with pain, distinguishing it from mild bruising because of hematoma of the tissues. The following diagram (See Fig. 9) demonstrates a plan to prevent and minimize injury and to hasten the process of healing should adverse effects occur. These strategies should be instituted immediately to prevent/limit further damage.

HA-injecting physicians need implement the treatment protocol in Figure 9 by creating a "kit" in the clinic so that hyaluronidase and 2% nitroglycerin paste are always available in the event of an emergency.

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