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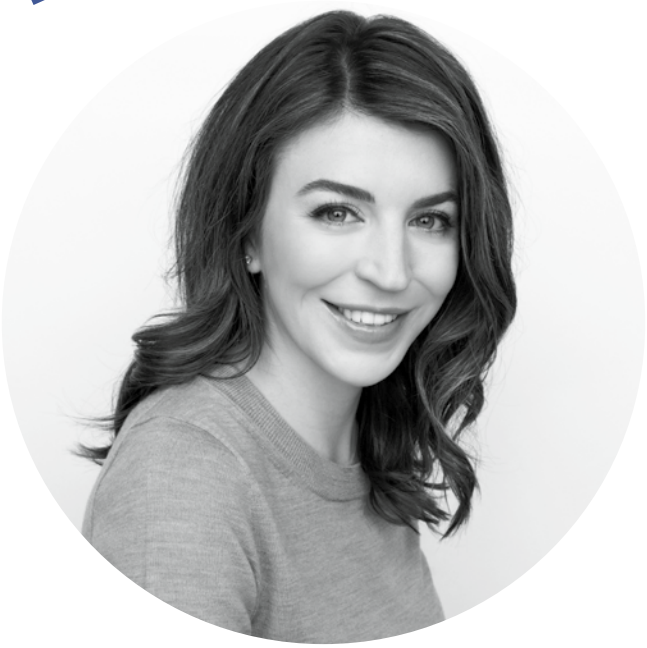

AN UPDATE ON COMPLICATIONS FROM FILLERS

Filler injections are one of the most popular cosmetic procedures performed worldwide in part due to their ease of use, as well as efficacy and safety. However, complications can occur, and it is important for injecting practitioners to have a thorough knowledge of these complications **(Table 1)** to both prevent and manage adverse events.

TYPE	DESCRIPTION
EARLY INJECTION SITE REACTIONS	SWELLING, ERYTHEMA, PAIN, AND BRUISING
TECHNIQUE AND PLACEMENT RELATED	NODULES, BEADING, TYNDALL EFFECT
DELAYED NODULES	INFECTIOUS, BIOFILMS, GRANULOMAS, INFLAMMATORY/IMMUNE-MEDIATED
VASCULAR	SKIN NECROSIS, BLINDNESS

Table 1: Filler Complications

Early Injection Site Reactions

Injection site reactions are common and include erythema, pain, swelling, and bruising. These reactions typically resolve within one to two weeks. Strategies to reduce these risks include minimizing the number of skin punctures and applying cool compresses or ice.[1] Bruising can be limited by avoiding blood-thinning medications or supplements for at least 7–10 days prior to injection. Using a small gauge needle, cannula, and injecting slowly with small volumes can further reduce bruising. However, bruising may occur despite the best techniques and can be treated with intense pulsed light, pulsed dye lasers or potassium titanyl phosphate (KTP) lasers, which target the extravasated hemoglobin as a chromophore.[2] Superficial bruising can lighten within a day following laser or light-based treatment.

Technique and Placement

Inappropriate or uneven placement of fillers may result in palpable nodules and papules. Injecting hyaluronic acid (HA) filler too superficially may lead to beading or a blue-grey discoloration secondary to the Tyndall effect.

Hyaluronidase

One advantage of HA fillers is that they are reversible, and hyaluronidase is an enzyme that can be used to dissolve filler to resolve papules, nodules, Tyndall effect, or vascular compromise. Different formulations are available, which makes it difficult to establish standardized dosing. An in vitro, dose–response study suggests that Juvederm® is more resistant to hyaluronidase compared to Restylane®.[3] A commonly articulated approach is 5-10 units of hyaluronidase are needed to dissolve 0.1 mL of filler and it should be noted that more hyaluronidase may be required for the highly cross-linked fillers. In the case of impending necrosis, a minimum of 500 units of hyaluronidase should be used.[4] Evidence has shown that degradation was similar when hyaluronidase was administered (10 U/0.1 ml of filler) at four days or four weeks post-filler injection, indicating that tissue integration did not impede the ability of hyaluronidase to degrade HA filler.[5]

The published incidence of allergic reaction to hyaluronidase is low at 0.05%.[6] Bee and wasp venoms contain hyaluronidase and there is a theoretical cross-reactivity in patients who have an allergy. For patients who have had severe reactions or anaphylaxis to bee or wasp stings, a skin test can be considered prior to treatment for non-urgent indications.[7]

Delayed Nodules

Delayed nodules secondary to filler have multiple possible etiologies and are difficult to diagnose without histopathology or culture results. Delayed nodules may result from infections, biofilms, foreign body granulomas, or inflammatory/immune-mediated causes.

Infection following filler treatment is uncommon but can occur with any procedure that breaks the surface of the skin. Potential infectious etiologies may be bacterial, fungal, or viral. To minimize the risk of infection, the skin should be cleansed prior to injection with an antimicrobial agent such as isopropyl alcohol, chlorhexidine or Techni-Care®. Infections may present as tender erythematous fluctuant abscesses or nodules. Systemic symptoms such as fever may occur but are rare. A lesion suspected of being an infection should be cultured or biopsied. Treatment options include incision and drainage and/or broad-spectrum antibiotics until the culture results are confirmed.[8] Trauma from the filler injection can also lead to reactivation of herpes virus infection. If the patient has a history of cold sores and is receiving treatment in the perioral area, prophylactic antiviral treatment should be considered.[2]

Biofilms have been implicated as one potential cause of delayed nodules after filler. Bacteria are thought to coat the filler when it is injected, forming a biofilm. Biofilms secrete a protective matrix that allows them to adhere to surfaces resulting in a low-grade chronic infection that is resistant to the immune system and antibiotics. Cultures are often negative as standard culturing techniques are not sensitive enough to detect the microorganisms.[2] To reduce the risk of acquiring biofilms, it is important to avoid any contamination during injection. The skin should be thoroughly cleansed prior to injection and makeup and any other potential contaminants on the skin should be removed. Sterile technique should be used when reconstituting or diluting fillers.[9]

Foreign body granulomas are another potential cause of delayed nodules. Synthetic fillers can act as foreign bodies, stimulating a host response and granulomatous inflammation. This presentation, though rare, has been reported and confirmed with histology.[2] Granulomatous reactions may be seen more commonly with permanent filler.

Inflammatory or immune-mediated causes of delayed nodules have become increasingly recognized in the literature. HA fillers are not typically considered immunostimulatory because HA is a natural component of the dermis and has no species specificity. However, both immediate and delayed hypersensitivity reactions have been described with HA fillers.[11] The time to onset of delayed nodules ranged from one month to three years after HA implantation.[12] It has been proposed that immune reactions could be due to residual proteins or impurities resulting from the manufacturing process; however, the manufacturing process has improved with time.[8] While HA injected on its own does not act as a foreign antigen, more recent data suggests that it has a larger role than an inert structural component. Data has also indicated that low-molecular weight HA (LMW-HA) may be pro-inflammatory and can trigger the immune system by direct interaction with cellular receptors or via inflammatory contaminants such as protein or endotoxins.[13] This may be a potential cause of some of the delayed reactions seen with fillers designed with Vycross® technology. The etiology of these delayed nodules is likely multifactorial. It is possible that as the filler breaks down, particularly over the three to five-month post-injection period, an increased exposure to LMW-HA fragments or catabolic by-products can stimulate an immune response. Having an inflammatory response to filler may be more common when the immune system is

primed after a triggering event, such as a recent infection like influenza or a dental procedure.[9]

Treatment of delayed nodules should be guided by any investigational results such as histopathology or culture. These nodules may resolve spontaneously; however, removal of HA filler by hyaluronidase, or incision and drainage can be considered. Treatments that have been used for delayed nodules include but are not limited to: intralesional hyaluronidase; topical, intralesional or oral corticosteroids; oral antibiotics; intralesional 5-fluorouracil; oral immunosuppressants; and lasers; or a combination of these treatments.[8] For suspected delayed inflammatory nodules from HA filler, treatment approaches include watchful waiting, intralesional hyaluronidase, oral prednisone (20–40 mg every morning for five to seven days), and/or intralesional triamcinolone acetonide (5–10 mg per ml, with repeat injections at two to four weeks as needed). If a biofilm is suspected, oral antibiotics for two to six weeks can be used.[9]

Vascular

The most serious potential complications from filler are vascular compromise with skin necrosis or blindness which may occur if filler is injected into the blood vessel resulting in an ischemic or embolic phenomenon. Blindness results from retrograde embolization of filler into the ocular vessels **(Figure 1)**.

Symptoms of vascular compromise include pain, blanching, duskiness, and reticulated violaceous erythema. This can progress to necrosis and scarring. Visual complications after filler may present with immediate vision loss, ocular pain, headache, nausea, or vomiting. Further, patients

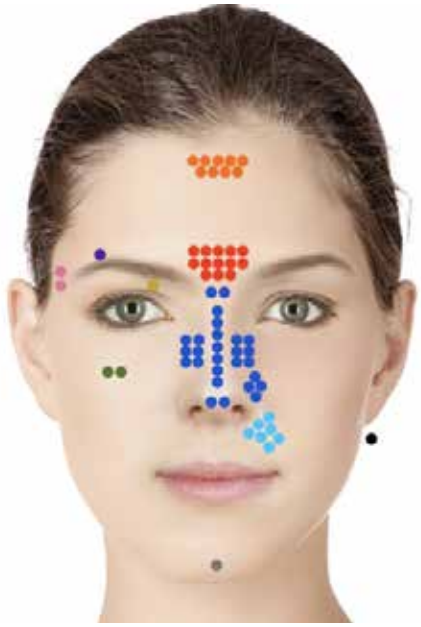

Figure 1. Location of filler injection resulting in visual complication. The single black dot represents a case where the anatomic location of injection was not specified. Originally published in Beleznay et al[22]; reprinted with permission.

may have central nervous system complications including infarction and hemiplegia in association with blindness. In our original review of the global literature, there were 98 cases of blindness reported. Autologous fat was the most common filler type to cause this complication (nearly 48%) followed by HA (23.5%). The sites that were high risk for complications were the glabella (38.8%), nasal region (25.5%), nasolabial fold (13.3%), and forehead (12.2%), but virtually every anatomic location where filler is injected in the face is at risk for vascular compromise.[14] Subsequently, we updated the review of blindness cases published in the literature and there were an additional 48 cases between 2015 and 2018. HA represented 81.3% of the cases in this review with the most common location being the nasal region (56.3%), glabella (27.1%), forehead (18.8%), and the nasolabial fold (14.6%).

Vascular Anatomy

Having an understanding the vascular anatomy prior to injection is critical to prevent these complications **(Figure 2)**. Most of the blood supply to the face is through the external carotid artery, except for a region of the central face encompassing the eye, upper nose, and central forehead. The ophthalmic artery, a branch of the internal carotid, provides the blood supply to this area.[15] The ophthalmic artery branches into various arteries including the supraorbital, supratrochlear, and dorsal nasal artery. The facial artery branches off the external carotid artery and passes over the jaw anterior to the masseter muscle and proceeds in a superior and diagonal direction. The facial artery becomes known as the angular artery in the region of the nasolabial fold and has variable patterns as it continues superiorly. It anastomoses with other facial vessels including the dorsal nasal artery connecting the external and internal carotid system.[16]

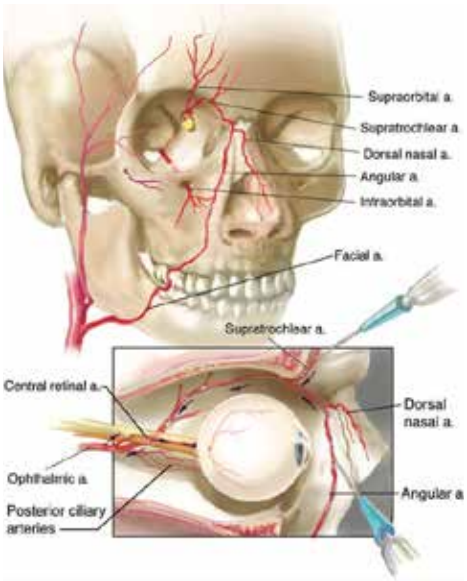

Figure 2. Vascular anatomy of the face. A selection of facial vessels are highlighted here. This is one depiction of the blood vessels of the face and there is individual anatomic variability. Inset demonstrates the mechanism of action of filler-induced blindness. In this diagram, filler is shown being injected directly into the supratrochlear artery or into the angular artery, which anastomoses with the supratrochlear artery. From here filler can travel retrogradely, as shown by the arrows, into the ophthalmic artery and its branches, blocking blood supply to the retina and causing visual complications. Originally published in Beleznay et al[22]; reprinted with permission.

It is important to understand the depth and location of vessels in high-risk sites. In the glabella and forehead, the two major arteries are the supratrochlear artery, which is typically found along the medial canthal vertical line, and the supraorbital artery, which is more lateral in the region of the medial iris. Both of these arteries start their course deep and become more superficial approximately 15–20 mm above the supraorbital rim. They remain in the subcutaneous plane as they travel superiorly on the forehead. Therefore, injections at the levels of the supraorbital rim or within 2 cm of that location should be quite superficial if attempted, keeping in mind this area is very high risk. However, injections more superiorly on the forehead should be deep in a supraperiosteal plane.[17] In the nasal region there are many anastomotic vessels and therefore several reports in the literature suggest that the safest plane to inject filler is deep in the more avascular supraperiosteal plane.[18] If the patient has had previous surgical procedures to the nose, filler injections should be avoided or carried out with extreme caution. In the medial cheek, periorbital area, and nasolabial fold the angular artery is the high-risk artery. The angular artery can have variable patterns after it branches off the facial artery and can be located in the subcutaneous layer, so caution is advised when injecting in this region. With the rich vascular supply of the face and multiple anastomoses, it is very important to understand the location of vessels and appropriate depth of injection.[14]

Prevention

Strategies to prevent vascular complications are critical. It is most important to have a firm understanding of the vascular anatomy and depth of injection, particularly in high-risk sites such as the glabella, nasolabial fold, and nose. Choosing a reversible HA filler allows for treatment with hyaluronidase and the possibility of reversing vascular occlusion if used in a timely manner. Other strategies to implement include using low volumes of product, injecting slowly, and using a small gauge needle or cannula. Cannulae are blunt tipped and many believe that they reduce the risk of vascular injury, particularly in high-risk areas. Key prevention strategies are highlighted in **Box 1**.

Box.1 Strategies to Prevent Vascular Compromise[14,19]

- Know the location and depth of facial vessels
- Inject slowly and with minimal pressure
- Inject in small volumes
- Move the needle tip while injecting to avoid injecting a large bolus in a vessel
- Consider aspiration prior to injection
- Use caution if injecting in a location where prior surgical procedure
- Consider using a cannula

Treatment

Treatment should be instituted immediately at the first sign of vascular compromise. It is important to recognize, however, that treatment recommendations are not based on a large body of evidence. The goal of treatment is rapid restoration of perfusion. Key management strategies for vascular compromise with skin sequelae **(Box 2)** and ocular complications will be discussed.

If blanching occurs while injecting filler, immediately discontinue the injection. If the complication occurs with an HA filler, injection of hyaluronidase is recommended. It has been shown that hyaluronidase can diffuse through the blood vessel walls without needing to be directly injected into the vessel.[20] A published protocol by DeLorenzi suggests the injection of 500 units of hyaluronidase every hour or so until the ischemia is resolved (skin colour has returned, and capillary refill time has returned to normal) for a single affected area. For two affected areas 1000 units should be used and 1500 units used for three areas. As long as treatment is completed within 72 hours of the onset of ischemia, successful resolution is common.[4] In addition, treatments that should be initiated include warm compresses and massage. Other potential therapies include topical nitroglycerin paste, aspirin, oral prednisone, hyperbaric oxygen, and low molecular weight heparin. A thorough individual assessment and treatment plan with close follow-up should be initiated for each patient to ensure optimal outcomes.[19]

Box 2. Treatment of Vascular Compromise with Skin Sequelae[19]

- Stop the injection immediately
- Inject hyaluronidase if an HA filler was used
- Apply warm compresses every 10 minutes for the first few hours
- Vigorous massage
- Consider administering aspirin, 325 mg under tongue immediately and 81 mg daily thereafter
- Follow patient daily until improvement. Provide them with clear written treatment instructions

Management of blindness from filler is more challenging as there are few reported successful treatments and no consistent evidence-based treatment

strategies. In addition, there is a strict timeline, ideally within 15 minutes, as the damage secondary to retinal ischemia is more likely to be irreversible beyond this timepoint.[21]

First and foremost, if the patient complains of ocular pain or vision changes, the injection should be stopped immediately. The patient should be immediately referred to an ophthalmologist. If an HA filler was used, hyaluronidase should be injected into the skin at the site of injection and along the path of anastomosing arteries. Injecting hyaluronidase into the area of the supraorbital or supratrochlear notch, in an attempt to cannulate the arteries, and push the hyaluronidase retrograde may also be considered. Retrobulbar or peribulbar injection of hyaluronidase has been described as a method of getting hyaluronidase closer to the area of blockage. It is controversial whether this technique is successful at salvaging vision loss and which clinician(s) should be attempting this technique. However, there have been several published and anecdotal reports of success from this technique. Other treatments that can be instituted in the office include topical timolol, rebreathing into a paper bag, ocular massage, and oral aspirin. Treatments that may be considered by the ophthalmologist to decrease intraocular pressure include anterior chamber decompression, mannitol, and acetazolamide. There have been many other treatments reported, but none have been consistently successful in restoring vision.[22]

Conclusion:

As the use of soft tissue fillers continues to rise, it is important to be aware of complications. To minimize any adverse events, a thorough understanding of facial anatomy and proper injection technique is critical. Injectors should be aware of both prevention and management strategies to minimize complications and improve patient outcomes.

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