Cosmetic Medicine

Continuing Medical Education Article

Complications of Injectable Fillers, Part 2: Vascular Complications

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Abstract
Accidental intra-arterial filler injection may cause significant tissue injury and necrosis. Hyaluronic acid (HA) fillers, currently the most popular, are the focus of this article, which highlights complications and their symptoms, risk factors, and possible treatment strategies. Although ischemic events do happen and are therefore important to discuss, they seem to be exceptionally rare and represent a small percentage of complications in individual clinical practices. However, the true incidence of this complication is unknown because of underreporting by clinicians. Typical clinical findings include skin blanching, livedo reticularis, slow capillary refill, and dusky blue-red discoloration, followed a few days later by blister formation and finally tissue slough. Mainstays of treatment (apart from avoidance by meticulous technique) are prompt recognition, immediate treatment with hyaluronidase, topical nitropaste under occlusion, oral acetylsalicylic acid (aspirin), warm compresses, and vigorous massage. Secondary lines of treatment may involve intra-arterial hyaluronidase, hyperbaric oxygen therapy, and ancillary vasodilating agents such as prostaglandin E1. Emergency preparedness (a “filler crash cart”) is emphasized, since early intervention is likely to significantly reduce morbidity. A clinical summary chart is provided, organized by complication presentation.

Keywords
soft tissue filler, HA filler, hyaluronic acid, hyaluronidase (HYAL), hyaluronic acid complications, dermal fillers, embolia cutis medicamentosa, Nicolau syndrome, Freudenthal syndrome, vascular complications, intravascular injections, cosmetic medicine

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LEARNING OBJECTIVES
The reader is presumed to have general knowledge of dermal fillers and their application in treating rhytids and restoring facial volume, as well as a broad understanding of facial anatomy, including detailed anatomy of tissue planes and fat deposits. After studying this article, the participant should be able to:

1. Describe the signs and symptoms of accidental intravascular injection
2. List the associated risk factors and describe risk reduction techniques
3. List the treatment options to be implemented following diagnosis of intravascular complications

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Of all possible complications following aesthetic treatment with dermal fillers, perhaps none is as dramatic or terrifying as accidental intravascular injection, which involves partial or complete vascular compromise resulting from filler injection into the arterial system. This complication may result in either local and/or distant ischemic necrosis. Considering that patients are treated with fillers for relatively minor aesthetic complaints, the risk and severity of this complication is so out of proportion with the expected outcome as to be profoundly alarming to physicians. Fortunately, these adverse events (AE) are extremely rare. However, with the increasing popularity of filler treatments, the prevalence of rare complications will increase in proportion to the number of procedures as a statistical certainty. Numerous dermal filler agents have been approved by the US Food and Drug Administration since the 1980s, and accidental intra-arterial injections have been reported for all of them. This Part 2 follow-up article contains information about clinical signs and symptoms of accidental intravascular occlusion and a cohesive description of the pathophysiology of these AE, the goal of which is promote an understanding of the clinical strategies that can reduce risk.

Additionally, the information in this article should help physicians to increase patient safety by promoting emergency preparedness in clinics and offices providing these treatments. Private surgical facilities that promote cardiac emergency training and have in place emergency cardiac drugs and defibrillators have reduced cardiac morbidity and mortality. It is hoped physicians providing aesthetic filler treatments will take up the cause of accidental intravascular injection, educating themselves and their staff in early recognition and treatment of these complications, thereby reducing patient morbidity. Using the cardiac analogy, a “filler crash cart” may help ameliorate the outcome of these AE. As with all complications, prevention should be the primary goal.

Finally, this article contains a discussion of the most serious complications of dermal fillers—namely, vascular complications—sometimes appearing in the literature as embolia cutis medicamentosa (ECM), Nicolau syndrome, or Freudenthal-Nicolau syndrome.

Summarized clinical case reports found in the medical literature are presented, as well as cases seen by the author in cooperation with manufacturers, colleague clinicians, and other referral sources in his capacity as medical director.

A major problem the author has encountered is that physicians generally have been quite reluctant to report in medical journals these filler-related complications, despite that these complications do not seem to be directly related to the injector’s expertise. Such complications happen even to physicians who have successfully treated thousands of patients for many years without encountering any such problems previously. In short, physicians should not consider such problems a source of embarrassment or a sign of poor technique.

The true prevalence of these injuries is difficult to ascertain as a result of this underreporting. The author’s personal discussions during coffee breaks at national and international meetings (and even small regional meetings) almost always uncover new, never reported cases being relayed. Although manufacturers are compelled by the FDA to carefully record and report AE, without the initial physician’s cooperation, these databases are incomplete. Many physicians elect not to participate in the reporting process. Complications data could be improved by mandatory reporting of all AE, but unfortunately there seems to be little current impetus for such a requirement.

**HISTORY**

In 1924, the brilliant young Freudenthal reported on full-thickness dermal necrosis associated with intramuscular injection of oily bismuth suspension, which was used to treat syphilis at that time. He described the histological appearance of these suspended particles deep within the cutaneous arteries, distant from the injection site. This condition was also described by Nicolau the following year, and the syndrome more often bears his name, despite Freudenthal’s precedence in the literature.

The essential difference between those cases of ECM and the pathophysiology seen with dermal filler vascular obstruction is that the former often involves inflammatory pathways being activated by the injected material, whereas the latter typically involves a more purely mechanical vascular obstruction. (Although some fillers may promote blood clotting, hyaluronic acid [HA]–based dermal fillers by design are minimally reactive in tissues.) The phenomena are similar in that the inciting event is accidental intravascular injection, followed by some degree of intravascular transport, finally resulting in vascular obstruction, ischemia, and so on, such that the ultimate clinical presentation is the same. The reader is cautioned to be mindful of this difference in causation, because the drugs reported to cause ECM may have quite specific correlations regarding the drug amounts (which vary from drug to drug) that provoke the problem. Similarly, different fillers may have widely ranging effects within the vascular system, depending on their propensity to activate the clotting mechanism—for example, collagen or fat. Clearly, dermal fillers which have the ability to incite an active intravascular inflammatory reaction can result in higher degrees of vascular obstruction beyond the purely mechanical effect seen with typically noninflammatory HA fillers. Of specific interest to this discussion, some HA may even have significant heparin-like activity, in contrast to collagen’s clot-promoting action.
Obstruction of dermal blood vessels is uncommon but is seen with various disease entities associated with vascular occlusive diseases. The clinical presentation of dermal ischemia may involve livedo reticularis, erythromelalgia, ulceration, or frank dermal infarct. Livedo (from the Latin lividus, of bluish or leaden color) reticularis (from the Latin root rete, net) appears as a macular, violaceous, net-like skin discoloration, which is usually a benign effect associated with exposure to cold. Almost 100 different diseases and drugs can also promote this blotchy appearance, due to venodilation caused by blood deoxygenation in the venous plexus. In ECM cases, livedo reticularis is observed at the edge of necrotic areas. In cholesterol emboli proximal to the skin, crystals are typically found in the arterioles and small arteries in the lower dermis or subcutis. This same pathology has been observed with dermal fillers. The degree of observed histopathological change in tissues affected depends on whether the process is acute, as with dermal fillers, or chronic, as part of an underlying disease process. In acute cases involving otherwise healthy individuals, apart from the filler product’s presence within the blood vessels, there may be few other clinical or histologic findings of note (excepting changes due to ischemia or infarction).

Due to arterial compromise, the pathology of vascular complications involves tissue anoxia and possible progression to necrosis (Table 1). The essential component common within this group is accidental intravascular filler injection into the arterial system, resulting ultimately in obstruction of the arterial blood supply. Depending on the nature and quantity of the filler agent, outcomes of differing severity are seen. For example, severe, dramatic complications involving extensive facial necrosis and requiring flap reconstruction have been reported with polymethylmethacrylate (PMMA) microspheres (Artefill, Suneva Medical, San Diego, California; Artecoll, Rodil Medical, Oroklini, Cyprus). However, many other commonly injected medications (including triamcinolone) have been involved in serious AE, resulting in extensive tissue necrosis, blindness, and stroke.

Why some fillers cause greater degrees of vascular compromise than others when administered in similar volumes remains unclear. This may pertain to a filler’s particular ability to activate an inflammatory process or, alternatively,
activate the clotting system—or both—thus resulting in an irreversible progression to frank necrosis of the involved tissues. A more likely possibility is that some fillers, because of particle size, are able to travel further down vascular pathways, to the point where the obstruction occurs. In the case of PMMA-based fillers, collagen simultaneously activates the clotting system. The phenomenon at the outset involves accidental intra-arterial injection; subsequently, the material travels with the blood throughout the arterial system, being carried to progressively smaller vessels. Although in ECM, some medications may cause severe inflammation and injury to the arterial lining (with associated edema progressing to complete arterial obstruction), volumizing HA filler products are typically well tolerated. Thus, their mechanism of causing ischemia is generally based on simple mechanical obstruction of the arterial blood supply. This mechanism is exploited in the treatment of vascular tumors via the transarterial chemotherapeutic agents, is administered—a procedure commonly employed in therapeutic radiology departments worldwide.

Accidental venous injection, as opposed to arterial injection, is unlikely to cause any obvious clinical symptoms given the quantities generally used by physicians and surgeons. This article deals only with ECM caused by filler products (defined as accidental intra-arterial injection of filler products). Risk factors associated with this phenomenon are shown in Table 2.

Arterial vessels traverse many of the areas commonly treated with fillers. For example, the labial artery is very close to the surface (Figure 1), and it is obvious how a fine, sharp needle could enter the artery, causing accidental occlusion with a dermal filler agent. The human face is endowed with a rich vascular network, and given the numerous collaterals and anastomoses present between vascular territories, it presents a target-rich environment. Additionally, the presence of collateral pathways is also protective: obstruction of any particular pathway often opens alternatives to provide satisfactory blood supply. Knowledge of the location, distribution, and pathways of the face’s main vessels is essential for clinicians involved in this type of work. The rich anastomoses between the nose’s external and internal carotid arteries can cause paradoxical complications. For example, a recent case involved fat injection into the right nasolabial fold that resulted in immediate blindness in the left eye (the contralateral eye), despite quick assistance by a highly regarded tertiary care ophthalmology team.

This mechanism of intravascular transport of fillers through rich vascular anastomoses is important to understand, however, since it explains how tissue embolization may occur proximal, distal, and even contralateral to the

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Description</th>
<th>Clinical Considerations</th>
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<tr>
<td>Site</td>
<td>Deep injection of filler products at or near the site of named vessels. Needle aspiration may or may not show any flashback of blood.</td>
<td>Exercise increased caution near facial artery, angular artery, along nasolabial fold, the nose, and glabellar areas. Intimate knowledge of the location-named facial vessels is mandatory for injectors.</td>
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<tr>
<td>Volume</td>
<td>The volume of product injected into any one area is a risk factor, since larger amounts of product can cause a progressively greater degree of arterial obstruction. Safer practice is to inject no more than 0.1 mL into any 1 location, and change the position for further injections.</td>
<td>Attempts to clear a needle obstruction by increasing the syringe pressure is a risk factor, since accidental discharge of a large volume of material can result, with disastrous consequences if the needle tip is in the lumen of an artery. Purposeful large-volume injection (Lake Technique) is also a risk factor for the same reason.</td>
</tr>
<tr>
<td>Small sharp needles</td>
<td>Small-gauge sharp needles are more likely to penetrate the lumen of an artery than are larger needles. Aspiration of arterial blood through a narrow-gauge long needle is an unreliable indicator.</td>
<td>Larger caliber needles are more likely to have “back flash” of blood following aspiration. Although aspiration prior to injection is good practice, viscous filler material may not allow arterial blood to flash back into the syringe.</td>
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<tr>
<td>Previous scarring</td>
<td>Deep tissue scars may stabilize and fix arteries in place, making them easier to penetrate with small sharp needles. This may also occur when injecting sites where arteries pass through bony foramina or deep fascial structures.</td>
<td>In fatty tissues, thicker walled arteries may roll out of the way when prodded by larger needles, as attested to by those experienced in microvascular surgery. Fixation by scarring holds the vessel in place, making it easier to penetrate.</td>
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<tr>
<td>Blunt cannulae</td>
<td>Blunt cannulae may reduce—but not eliminate—the risk of accidental intra-arterial injection, especially in the presence of previous scarring (following years of filler treatments in the same area, for example). There have been several reports of accidental intra-arterial injection with blunt cannulae.</td>
<td>Some cannulae possess a bullet tip, and although they have a side port, these fine cannulae (eg, smaller than 27 gauge) can penetrate arterial walls. Larger diameter cannulae with a rounded tip are less likely to penetrate. There are no LOE 1 or 2 clinical reports that support treatment via cannulae at present, and the author knows of accidental arterial injections that have occurred despite cannulae application.</td>
</tr>
<tr>
<td>Composition of filler material used</td>
<td>Permanent fillers have no means of dissolving the material. Some fillers promote immediate clotting.</td>
<td>HA products have the advantage of being hydrolyzed by hyaluronidase.</td>
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*Although successful treatment depends on aspects of technique, intimate knowledge of the facial arteries’ surface anatomy is essential in avoiding intra-arterial injection.*
site of injection. This mechanism may explain puzzling cases of distant necrosis in adjacent vascular areas. Depending on the amount of material injected; its viscosity, cohesion, and other rheological properties; as well as the pressure applied, the filler may flow retrograde to the arterial blood flow. Thereby, the product moves through more proximal collateral blood vessels and then to regions distant from the original injection site (Figures 2 and 3).

Let us ignore these more complex cases for the moment and consider the much more common and direct episodes of ischemia. Regardless of the filler product’s path within the arterial system, the material injected is eventually carried along with the blood flow to progressively smaller arteries, then arterioles, and finally toward the capillary bed. If only a tiny amount is injected, it is quite possible the material will lodge in a location where the collateral vessels still manage enough blood supply such that minimal or no ischemia results. The rich vascular network bypasses the obstruction so completely that the accident never manifests itself clinically.

Human skin’s cutaneous microvasculature is organized into 2 horizontal, parallel plexuses consisting of 3 segments: arterioles, venules, and the interposed arterial and venous capillaries. Capillary loops extend into the dermal papillae from the upper plexus. The lower plexus is found at the dermal-subcutaneous interface, rising directly from the perforating branches from subcutaneous fat. Arterioles and venules from this structure are directly connected to the upper plexus, where most of the microvasculature is located (1-2 µm below the epidermal surface). In terms of internal diameters, the arteriolar vessels in the papillary dermis are approximately 17 to 22 µm, decreasing to capillary size of 4 to 6 µm, and then increasing again to post-capillary venules of 10 to 15 µm. Decades ago, physiologists realized the skin’s extensive blood supply far exceeded its nutritional requirements, surmising correctly that this organization helps control body temperature. As the largest proportion of vessels within the papillary dermis, postcapillary venules constitute the site both where inflammatory cells migrate from the intravascular space into the interstitial space and where acute inflammation—increased vascular permeability—occurs.

The overall structural anatomy of the 2 blood vessel layers is such that the vessels supplying the superficial plexus from the hypodermis create small conical zones, centered on the feeding vessels from the lower plexus. When
viewed 2-dimensionally from the surface, the disks forming each cone’s boundaries compose the pattern seen clinically during vascular obstruction. The disk pattern apparent on the surface delineates these conical drainage zones from the superficial to the deep plexuses. For example, the livedo reticularis pattern often present in cases of skin thromboembolism is related to slowing blood flow within the postcapillary venules. The clinical pattern observed is due to blood stasis in the dermal venules, and the bluish discoloration results from the dusky red-blue color of desaturated blood, optically filtered by the dermis and epidermis.

The caliber of the capillary loop vessels in the dermal papules is just wide enough for erythrocytes to pass through individually (with some deformation, since they are 7-8 µm in diameter). PMMA microspheres manufactured at 40 µm in diameter (Artefill), calcium hydroxyapatite (CaHA; Radiesse, Merz Pharmaceuticals, Greensboro, North Carolina) at 25 to 45 µm, or poly-L-lactic acid (PLLA; Sculptra, Valeant Aesthetics, Bridgewater, New Jersey) at 40 to 63 µm are all several times larger than the diameter of the smallest capillaries. Obviously, the end result of intra-arterial injection must be obstruction. Similarly, HA gels and many other dermal fillers would not be able to pass through such small vessels.

Differences in the structure of these gels may make a difference in their effectiveness for arterial occlusion. Polyphasic products (eg, Restylane; Valeant Aesthetics, Bridgewater, New Jersey)—a slurry of highly cross-linked gels and non–cross-linked lubricating HA—tend to spread out easily in vitro. In contrast, monophasic products (eg, Juvederm, Allergan, Inc, Irvine, California; Teyosal, Clarion Medical, Cambridge, Ontario, Canada), which consist of highly cohesive gels, tend to coalesce into a mound in vitro. In other words, such products do not spread out easily; they tend to retract. Composition factors may play a role in these products’ tendency to obstruct blood flow, but to date no study has been done. Nevertheless, there are definite distinctions between filler products; as evidenced by published case reports, their individual composition can and does make a clinical difference in the severity of obstruction and the likelihood of recovery with treatment.

A video demonstrating the differences in the in vitro behavior of the 2 product types, each of which has applications optimized for their specific properties, is available at www.aestheticsurgeryjournal.com. You may also scan the code on the first page of this article with any smartphone to be taken directly to the video at www.YouTube.com.

Additionally, physicians commonly reconstitute HA filler products to more favorably accomplish their goals, often compounding with local anesthetics or normal saline to reduce the HA concentration. Such mixtures thereby change the product’s flow characteristics—and presumably also change its propensity to obstruct blood flow. Taken together, all these factors make it difficult to state with certainty which products are most likely to cause irreversible ischemia, should accidental intra-arterial injection occur. All that can be said at this point is that each product can and does differ in its tendency to cause vascular obstruction.

When compared with a filler’s composition (regardless of its components), the quantity of injected material is probably a much more important factor in vascular obstruction. The most severe cases have not uncommonly occurred from the accidental, catastrophic release of a large quantity (> 0.1 mL) of filler—the result of excessive pressure applied to a small-caliber syringe with a partially blocked needle. The signs and symptoms of arterial insufficiency following accidental intra-arterial injection are shown in Table 1, and the typical timing of subsequent events is shown in Table 3. The early phases have not all been observed directly in all patients, but enough similarities exist to allow these generalizations regarding phenomena observed following intra-arterial injection of filler materials.

Note the branch point is dependent on the quantity of filler material injected into the artery (Table 1), where
there is either the unfavorable pathway toward ischemia or, alternatively, the good pathway toward restoration, reactivity, and bounding return of the circulation. The latter is sometimes variably associated with ischemia-reperfusion injury.86-91

Skin blanching immediately following accidental intraarterial injection of filler is occasionally seen but is by no means universally reported (Figure 4). (Another example of blanching occurs when injecting local anesthetics.) The blanching phase may be either completely absent or last about a minute; it also may be attributed to effects of epinephrine on the skin, as with infiltration of wetting solution with epinephrine for liposuction.

The livedo reticularis pattern is commonly observed, and several clinical examples have already been published.92,93 As described above, the body’s extremities may exhibit a livedo pattern in response to cold. When seen facially in response to a filler injection, it appears to be a reliable sign of vascular compromise.

The initial presentation of these events may include pain and discomfort disproportionate to what is typically experienced following filler treatments, but this has changed significantly over the past few years as more clinicians adopt fillers compounded with local anesthetics. Confounding variables are common, and the presence of epinephrine in local anesthetics may confound the clinical picture. Localized color changes in the affected areas should raise the index of suspicion of vascular compromise. The immediate picture is not important, however. Rather, progression of the signs and symptoms, and their timing (Table 3), deserves the greatest scrutiny, with the objective of learning to recognize these AE early enough to circumvent sequelae of vascular obstruction.

Since Galen’s time, skin color has been used to evaluate physical health. Despite some limitations, capillary refill time has been used as a clinical test of perfusion for decades, especially for children. During the past 50 years or so, circulation also has been monitored via capillary refill in free tissue transfer or replantation.94 Generally, a 1- to 2-second capillary refill time in association with pink, warm skin is considered normal. Bluish skin with extremely fast capillary refill may signal venous insufficiency, and slow capillary refill with dusky or blue-black color may indicate arterial insufficiency.

Table 3. Typical Complication Progression After Accidental Intra-arterial Injection of Hyaluronic Acid (HA) Filler

<table>
<thead>
<tr>
<th>Clinical Findings</th>
<th>Timing</th>
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<tr>
<td>Blanching: invariably immediate, usually seen during the actual injection</td>
<td>Lasting seconds to tens of seconds</td>
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<tr>
<td>Livedo pattern or, alternatively, immediate reactive hyperemia if insufficient material injected to occlude the artery (typically &lt;0.1 mL for the angular artery)</td>
<td>Minutes, sometimes up to tens of minutes</td>
</tr>
<tr>
<td>Blue-black discoloration</td>
<td>Tens of minutes to hours</td>
</tr>
<tr>
<td>Blister/bulla formation</td>
<td>Hours to days</td>
</tr>
<tr>
<td>Skin breakdown, ulceration, demarcation, slough</td>
<td>Days to weeks</td>
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</table>

*Note branch point after initial blanching reaction of skin. If circulation is restored, skin usually exhibits reactive hyperemia (blushing), followed by return to normalcy. If vascular occlusion is significant, skin may show livedo, followed by other signs of ischemia.

Clinical examination of patients with arterial occlusion may demonstrate slow capillary refill, often associated with skin extremely tender to the touch (Figure 5). (Recall that pain symptoms are highly subjective.) When local anesthetics are given either for a local or regional block, or when a local anesthetic is formulated with the filler product, pain may be absent in the initial ischemic presentation until the anesthetizing effects have subsided. Capillary refill may also be unreliable, since the effects of ice, epinephrine, or other medications may mask signs and symptoms of underlying arterial insufficiency (Table 3). The patient shown in Figure 4 presented noticeable blanching following careful injection of CaHA. However, given the small quantity injected in the area, she did not have any lasting ill effects. This illustrates the importance of filler quantity used in any single site, as a larger amount of product undoubtedly would have had far more serious consequences.

The recommendation that fillers should be distributed via small boluses of 0.1 mL or less should be balanced by the risk of injecting a larger number of sites, along with the difficulty of getting reliable flashback into the syringe through fine needles filled with thick gels. This raises the issue about whether it is safer to inject larger quantities of material into fewer areas or to inject tiny amounts into numerous areas (presumably more vessels might be hit, statistically speaking). This question cannot be answered at present because of lack of clinical or laboratory data. However, it is known that accidentally injecting an artery with a large amount of material will certainly have devastating consequences, whereas injecting a tiny amount into an artery will usually not have any significant repercussions. Therefore, on balance, it is likely safer practice to inject tiny amounts (0.1 mL) into numerous areas.

The face’s vascular anatomy should be familiar to treating physicians, and during the pretreatment planning phase, proximity of susceptible vessels to common
Figure 4. This 62-year-old woman was injected in the nasolabial fold areas with calcium hydroxylapatite (Radiesse, Merz Aesthetics, San Mateo, California) compounded with 0.1 mL of 1% lidocaine without epinephrine. (A, C, E) She experienced immediate blanching of upper lip, nose, glabella, and left nasolabial fold region following injection of 0.1 mL filler. (B, D, F) Her appearance 10 minutes later shows some reactive hyperemia of the affected areas. This patient did not have any adverse consequences and made an uneventful recovery. (Photo courtesy of Dr Art Foley, Olympia, Washington)
treatment areas should be kept in mind. The external carotid branch to the face—namely, the facial artery—continues midface as the angular artery immediately subjacent to the nasolabial fold, an area frequently treated with fillers (Figure 6). The vessel continues toward the nose, where several collateral vessels conjoin the internal with the external carotid territories (Figure 7). The angular artery in particular is a site often affected, given the popularity of treatment of the nasolabial area. Injection of dermal fillers deep to the orbicularis oris or zygomaticus muscles in this region with sharp, fine needles may thus be considered a higher risk procedure (Figure 8).

There may be some question as to the pathophysiology of AE that involve cutaneous and subcutaneous necrosis. The author frequently hears that patients were “allergic” or demonstrated profound sensitivity to the filler or 1 of its components, resulting in skin slough. Clinical case studies of patients presenting with these symptoms have been analyzed, including biopsies of the affected arteries. These reports have shown foreign material present in the artery’s lumen, including thickening of the tunica intima, with corroborating 3-dimensional computed tomography (CT) angiography showing both vascular occlusion and compensatory dilation of collateral vessels. Given the serious nature of these events and the fact that “allergy” fails to explain the extent of necrosis—whereas arterial occlusion explains such complications perfectly—the author believes that the latter mechanism is beyond doubt. These studies also support the hypothesis that intra-arterial injection, as opposed to external vascular compression, is the root cause of decreased blood flow. Although conceivable that in some rare circumstances, external pressure from a filler agent can cause decreased blood flow, this does not appear to be the typical primary mechanism. In fact, trying purposefully to recreate such results in preliminary investigations with a rabbit ear model failed: only direct intra-arterial injection of dermal filler resulted in cutaneous necrosis. Although external compression may play a role in cases where large amounts of material have been injected under significant tissue tension where tissues are restricted from their normal elasticity by disease, trauma, or previous surgery (scarring), or when vessels pass through rigid fascial structures or bony foramina, the author does not believe this mechanism is supported by much clinical evidence.

Experimental evidence suggests that predisposed arterial anatomy is important, which may help explain the patterns of vascular injury seen in the literature: certain areas of the face—the glabella, for example—appear to be predisposed to injury. In fact, while developing an animal model of embolization with dermal fillers, Kim et al had to surgically ablate a collateral vessel in order to obtain necrosis with intra-arterial injection. This suggests that predisposed arterial anatomy is an essential prerequisite (given that filling the artery in question while the collateral vessel was intact did not result in necrosis).

In summary, the pathophysiology of vascular occlusion begins with immediate changes visible in the vascular system: initial blanching, followed by mottled discoloration called livedo reticularis. This is accompanied by pain, unless there is a nerve block or local anesthetic blocking the pain pathways. The resulting ischemia produces a dusky discoloration associated with sluggish or absent capillary refill after digital compression, as well as possible loss of function. In the case of retinal artery occlusion, a visual field defect may be present, and fundoscopy makes the filling defect evident. Treatment should commence without delay, especially if visual access is affected. Cutaneous ischemia is less of an emergency, and although full recovery without scarring has been achieved more than 24 hours after the AE, in general the sooner treatment is given the better. In a rabbit ear model, a 24-hour treatment delay resulted in necrosis.

RISK FACTORS

There are few consistencies in case reports in the literature. The main commonality is that a sharp needle—usually provided by the manufacturer along with the product—was used
to administer the filler. It can thus be argued that as much as the filler itself, needles are an essential prerequisite for an AE. It is easy to assume that narrow-gauge needles could easily enter an artery’s lumen, followed by an unknown quantity of filler material, to cause the mechanical disruption of circulation.

The first case reports of skin necrosis occurred with the first filler approved for general use: collagen. Hanke et al reported the incidence of localized tissue necrosis with Zyderm or Zyplast (Inamed Corp, Fremont, California) as 9 of 10000 cases (0.09%); over half the reported cases involved the glabella. These AE involved relatively superficial injection with a small-bore needle, and the glabellar region’s unique vascular distribution was deemed to play a role in the occurrence.

As products designed for deeper deposit into the subcutaneous tissues were developed, this article’s author became concerned about the risk of intravascular accidents and was involved in some of the initial clinical trials for a new, deep filler product from a major manufacturer in Sweden. In the initial stages, the author both prepared a report reviewing world literature concerning accidental intravascular injections and recommended the company place blunt cannulae for injection, rather than sharp needles. Unfortunately, the marketplace was not ready for blunt cannulae, and other companies developed products for deep injection while packaging them with sharp needles.

**Fat Grafting**

Reviewing some of the related literature in fat grafting yields insights into the problems that occur with fat injection. Fat grafting is not a new procedure by any means, with reports of its treatment applications dating back to the beginning of the 20th century. Coleman, more than any other surgeon, has promoted safe treatment with fat grafts, stressing from the beginning that sharp needles should be avoided, and warning of the risks of placing soft tissue fillers with sharp needles. In fact, all recommendations from his initial article are still valid today.

The quantity of material injected into the vessel is likely the most important factor in determining how much damage may occur. Clearly, if only a tiny amount is injected intravascularly, then only a small portion of the vascular structure can be occluded, thereby affecting a relatively small area. The normal collaterals present in the face would presumably make up for this deficit. Necessarily, as the volume of injected material increases, a larger portion of the vascular tree can be blocked, including the collateral

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**Figure 6.** (A) This 48-year-old woman received 1 syringe of Juvederm (Allergan, Inc, Irvine, California), a monophasic hyaluronic acid filler product, injected into the nasolabial fold area, including a small amount in the area deep to the alar margins bilaterally. She was given antibiotics and an injection of 150 IU hyaluronidase (HYAL, York Downs Pharmacy, Toronto, Ontario) immediately following the diagnosis of filler embolism, resulting in immediate significant improvement of her symptoms. She subsequently presented at 24 hours with continued tenderness and a small nodule palpable on the right nasolabial fold area adjacent to the nose. She was treated at that visit with another dose of 500 IU HYAL (York Downs Pharmacy, Toronto, Ontario) and local area massage. A common injury zone involves the angular artery; the most severe cases may involve both the upper and lower lips as well as the ala of the nose. (B) One week posttreatment, the patient’s indurated nodule had dissipated, and the area was no longer tender. The small scar at the alar margins was subsequently treated with a fractionated erbium laser (ProFractional; Sciton, Palo Alto, California) in the early collagen remodeling phase to good effect.
vessels. Accidental injection of more than 0.1 mL appears to be a clinical requirement for substantial injury, but obviously this also depends on the microcirculation’s structure, the presence or absence of collaterals, and the filler composition (ie, its ability to promote clotting and/or inflammation within the vessels). Injection of smaller quantities does not seem to result in significant arterial blockage in most regions; however, the region being treated is a critical consideration (eg, the glabella, as noted above).

Whereas one-tenth of a milliliter might not cause any significant problems in an area with abundant collateral circulation, this volume is devastating in the retina (Figure 8). Because any amount of filler could easily be considered problematic when based on various specific end arterial systems, the point here is to consider the most general case. Good practice minimizes the quantity being injected and the pressure applied at any single point, regardless of the injection site, since a large bolus entering the vascular system on the arterial side may potentially cause extreme harm.76,102

By means of illustration, let us follow a bolus of product injected first into a vein. The bolus would travel with the blood flow—namely, toward veins of increasing caliber—until it reached the vena cava and then the right side of the heart, finally coming out in the pulmonary artery. It would then become trapped somewhere in the pulmonary vascular tree, where it would be filtered out at the capillary level—or sooner, depending on its viscosity. A small amount of HA in a vein would be filtered out in the pulmonary circulation, likely with minimal sequelae in the quantities typically administered. It would be possible for some material to enter into the arterial side and thus cause serious embolic phenomena if there was communication between the left and right sides of the heart, as in cases of atrial septal defect, patent foramen ovale, and so on.

In contrast, let us examine this same bolus, injected into the glabellar region—had it entered, for example, the supraorbital artery. Because of pressure at the end of the needle, the product would likely flow retrograde to the blood at first, namely into the ophthalmic artery (Figure 8). Once there, the blood circulation would carry the bolus toward multiple egresses. If some product entered into the relatively small central retinal artery (Figure 7), then the material could lodge in the retina, causing blindness. Some product could also be carried forward to other vessels, not just back to the supraorbital vessels. An entire region may thus become contaminated with product.68

Angiosomes

The body is divided up into relatively discrete composite blocks of multiple tissues called angiosomes.103 Vascular accidents tend to involve these structures, and multiple tissue levels are often affected. Depending almost entirely on the amount of material injected into the vascular system, skin, subcutaneous fat, muscle, tendons, and even bone may be affected by these accidents. Physicians commonly misunderstand that only skin is affected in these AE. Rather, multiple layers of tissue are commonly affected at the same time. This often creates treatment problems, since simple skin grafts may not be an option because of the lack of a suitable graft bed. Axial pattern flaps may be required for tissue coverage.

Needle Size

Clinicians often favor small needles for treatment of rhytids. However, again, smaller needles are more likely to enter the lumen of a small vessel and are therefore more likely to cause an intravascular event. This is especially true when wielding small needles for deep volumizing treatments, since larger vessels are typically found in anatomically deeper structures. Larger bore needles tend to either roll arteries out of the way or side-cut them (causing significant bruising), rather than penetrating cleanly into the lumen. Smaller, extra-sharp needles tend to penetrate the vessel wall more easily and thus present a higher risk, especially if the vessel is in a location of restricted mobility.

Presence of Scars in Treatment Area

Physicians who have performed microsurgery know it is relatively difficult to get a needle into a small artery—such
as a digital artery—when it is dissected out. However, when
the injection site is near a point of fixation, ligament, or scar,
penetrating the artery becomes relatively easy, since the
artery will not roll out of the way. Thus, treating areas of
scarring (as from previous rhinoplasty or facelift) when
arteries may be fixed by surrounding scar tissues carries
higher risk than treating unscarred areas with fillers.

Multiple previous treatments with filler material also can
cause buildup of collagenous scar tissue in the treated area.
This is clinically self-evident, since patients with a long his-
tory of filler treatments often have a “gritty” subcutaneous
observed during retreatment injections. In fact, this may be
the source of long-term improvement seen in rhytids of
patients with long histories of repeated treatments.

**TREATMENT**

**Filler Crash Kits**

Just as it is important to reduce morbidity and mortality
from cardiac events by encouraging preparedness at point
of care, it is important to promote filler safety, specifically
by encouraging clinicians to prepare in advance for filler
emergencies. A “filler crash kit” consists of materials
needed to effect treatment in these clinical emergencies.

The treatment mainstay is hyaluronidase (HYAL),\textsuperscript{97,100,104-}
\textsuperscript{114} an enzyme that catalyzes HA hydrolysis.\textsuperscript{1} This is usually
supplied at 150 IU/mL, but different formulations, often
prepared locally by compounding pharmacies, may have
different potency, purity, and effectiveness. Furthermore,
different filler formulations exhibit different resistance to
degradation by HYAL in vitro.\textsuperscript{108,115,116} As conditions war-
tant, the dosage is titrated to clinical effect, rather than
absolute quantity of enzyme. HYAL anaphylaxis has been
reported in the literature,\textsuperscript{117} and as discussed in Part 1 of
this CME series,\textsuperscript{1} the presence of HYAL in the venom of
stinging insects may be the source of sensitization in
patients with wasp or bee sting allergy.\textsuperscript{118}

Treatment is accomplished with the diffuse injection of
HYAL into the tissues affected by ischemia. It is for the
most part unnecessary to get the HYAL into the vessel, as
it appears effective by diffusion. In fact, the author has
immersed fresh, human cadaver–sourced facial artery seg-
ments filled with HA (“hyaluronic acid sausages”) into an
HYAL solution and demonstrated dissolution of the gel
through the intact arterial wall within 4 hours. As soon as
HYAL has been injected into the subcutaneous tissues, it
tends to diffuse widely. Even a small degree of external
compression will allow the material to move subcutane-
ously. It is important to keep the material where the
obstruction is. If the filler has traveled to a distant location
from the original injection site, it seems most reasonable to
inject areas where the ischemia is present: for example, for
patients who had medication accidentally injected into a

![Figure 8](https://academic.oup.com/asj/article-abstract/34/4/584/2801399/584)
deltoid-area artery with subsequent ischemic changes in the hand and digits, treatment of the hand and digits would make the most sense clinically. However, in a recent case seen at a major center in the United States, the patient did not respond to repeated HYAL injections into the ischemic tissues and showed improved cutaneous circulation only after HYAL was injected directly into the affected artery (Dr C. J. Hwang, Jules Stein Eye Institute, personal communication, June 2012). To my knowledge, that was the first case report of intra-arterial HYAL as treatment for HA filler embolus, although this technique has been reported in the past for treatment of other disorders and was even used for treatment of acute myocardial infarction.

HYAL, by its very nature, can easily cross fascial planes and tissue structures by affecting the HA within the ground substance that glues our bodies together. Gentle massage is essential and sufficient to distribute the material, since gentle pressure will rapidly move the HYAL mixture diffusely throughout the tissues. A gentle pumping action may help break up and/or dissolve the blockage, opening collateral vessels that may carry fresh blood into the tissues. Warm compresses—not cold—may also help increase vasodilation. As in a cardiac event, administration of 80 mg aspirin may be helpful as an antiplatelet agent. Topical nitropaste administered judiciously to the affected area may similarly affect vascular dilation. The patient’s vital signs should be monitored appropriately when using vasoactive compounds. In severe cases, low-molecular-weight heparin and systemic anticoagulation may be helpful, but the author has no experience with this. Prostaglandin E1 (PGE1) has also been a clinical treatment to promote vasodilation—for example, in peripheral vascular disease. PGE1 may treat systemic or regional issues, and it has been reported as effective in acute retinal artery embolism. Some physicians have adjunctively treated filler embolisms with PGE1 (personal communications) but thus far there are no studies or reports in the literature. Systemic treatment is usually done in the hospital with the patient carefully monitored, as with all potent vasoactive drugs.

**Hyperbaric Oxygen**

Although no clinical studies yet support it, patients treated with hyperbaric oxygen (HBOT) along with the other methods described appeared to do better than patients who had not been so treated. Interpretation of these results is admittedly highly subjective, and the evidence is very weak. However, HBOT may prove helpful in treating ischemic injuries; in nicotine-treated animal models, HBOT has also proven effective in survival of random pattern skin flaps. Although unregulated in some jurisdictions, HBOT is FDA approved for the treatment of nonhealing wounds. The evidence in the literature for this application is somewhat mixed. Nevertheless, several authors have suggested HBOT for cases of dermal ischemia, although different protocols exist for treatment duration, pressure used, and number of sessions. Furthermore, different institutions may have differing treatment approaches; in many localities, HBOT is completely unregulated and may be conducted by nonphysicians. Regardless, in patients for whom the usual treatments did not completely restore normal skin circulation, physicians might consider using HBOT in a manner akin to its treatment of diabetic foot ulcers and similar wounds (for which there is literature support). Until further studies are done, it is difficult to say whether HBOT has a role to play in these injuries.

A full summary of information in this article, combined with information from Part 1, appears in Appendix 1, available online at www.aestheticsurgeryjournal.com. It is designed as a quick clinical reference guide to be used in the application of dermal fillers and the treatment of associated complications.

**CONCLUSIONS**

Ultimately, vascular complications are statistically rare following the injection of dermal fillers, but these complications are still prevalent in the population because dermal filler products are used so often. The risk is higher for these events when large bolus injections are sent deeper into tissues for volume enhancement and when smaller needles are used. Treatment begins with diagnosis of the event and should continue with administration of HYAL, aspirin, and topical nitropaste, along with the application of warm compresses and massage of the affected area. After initial treatment, if ischemia is still present, evidence, although weak, suggests that HBOT may benefit some patients (to salvage marginal tissue that might otherwise undergo necrosis).

**Disclosures**

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