Early ultrasound for diagnosis and treatment of vascular adverse events with hyaluronic acid fillers

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Background: Hyaluronic acid fillers are known for a reliable safety profile, but complications do occur, even serious vascular adverse events.

Objective: To improve the treatment outcome after a vascular adverse event with use of hyaluronic acid filler treatments.

Methods: Duplex ultrasonography is used to detect the hyaluronic acid filler causing the intra-arterial obstruction.

Results: If treated in time, 1 single treatment of ultrasonographically guided injections of hyaluronidase into the filler deposit will prevent skin necrosis.

Conclusion: Because the use of duplex ultrasonography adds extra essential information, its use may become an integral part of the prevention and treatment of injection adverse events. (J Am Acad Dermatol 2023;88:79-85.)

Key words: hyaluronic acid filler; ultrasound; vascular adverse event.

The popularity of robust hyaluronic acid (HA) fillers for facial contouring has risen dramatically in the past years, leading to their dominance in the aesthetic marketplace.[1] The HA molecule itself is a high-molecular-weight polysaccharide, which, at physiologic pH, binds water extensively and is completely resorbable; therefore, biochemically it is considered to be a safe compound.[2,3] However, even with safe degradable products, techniques, and treatment protocols, there is still the potential for adverse events. The Department of Dermatology, Erasmus Medical Centre (Rotterdam, The Netherlands) has established an outpatient clinic for filler complications that treats patients referred for both product-related (inflammatory responses and allergic reactions) and injector-related adverse events, which include overcorrection, injector nodules, malar edema, dislocation, accumulation of product (due to underlying muscle movement), and vascular events.[4-7] At the clinic, the frequency of intravascular complications leading to skin necrosis or blindness is, as of this publication (April 2019), twice per month. An increasing number of articles and guidelines have recently been published regarding these complications, including a safety warning of the US Food and Drug Administration on its website in 2015.[4-11]

One of the advantages of HA fillers is their dissolvability with hyaluronidase in the event of postinjection complications. Commercially available hyaluronidases serve as endoglycosidases that cleave the glycosidic bonds, inducing depolymerization[12,13] and a reduction of the normal high viscosity and lubricating action associated with the various HA roles in tissues. The clinical safety record in humans for hyaluronidase is well established, dating back more than 50 years, with allergic reaction

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Funding sources: None.
Conflicts of interest: None disclosed.
Accepted for publication July 11, 2019.
Reprints not available from the authors.

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Published online July 17, 2019.
0190-9622

https://doi.org/10.1016/j.jaad.2019.07.032

as the most serious complication. occurring at an incidence of 1:2000.[14,15]

For a vascular adverse event leading to skin necrosis, the use of hyaluronidase remains the first line of treatment.[9,11,13] Hyaluronidase has been shown to penetrate through thin vessel walls, but from a mechanical perspective will be limited in reaching the distal part of the HA filler obstruction in the blocked vessel.[16-18] Therefore, the current leading guideline involves the use of pulsed high-dose hyaluronidase in 1-hour intervals to bathe the obstructed vessels in a concentration sufficient enough to diffuse across the arterial wall and then break down the HA filler particles to metabolic products small enough to pass through the capillary system. For each ischemic area measuring 3 × 3 cm, a minimum of 500 IU of hyaluronidase is advised. It has also been recommended that the patient remain in the clinic for observation between pulses for anywhere from 3 to 8 treatment sessions until normal skin color returns.[18]

The outcome from this high-dose protocol has been shown to be very effective because the majority of patients treated did not develop necrosis, nor was there any residual scar tissue. However, there are several important drawbacks that should be noted with this therapeutic approach. The treating physician must rely purely on clinical observation; therefore, the precise location of the vessel obstruction within the zone of ischemia and the amount of filler are neither detectable nor appreciated. The hourly multiple pulsed injections of high-dose hyaluronidase over the ensuing hours can lead to skin trauma, is arduous, and often leads to exhaustion of both the patient and the physician, causing them to abandon the treatment until the next day.[18,19] Finally, the high dose of hyaluronidase required to penetrate the vessel wall increases the risk of possible retinal toxicity in the event of inadvertent intravascular deployment, especially in the periorbital region.

For these reasons, the use of a duplex ultrasonography (DUS) device was investigated for vascular mapping in high-risk zones before injection, as well as for determining both quantity and location of the HA to guide treatment in those cases of vascular compromise.[20] A comparison of current hyaluronidase protocols and ultrasonographically guided therapies are listed in Table I.

CAPSULE SUMMARY

- Vascular adverse events caused by hyaluronic acid fillers may lead to skin necrosis. To prevent necrosis, the use of hyaluronidase to dissolve the filler remains the first treatment option.
- Duplex ultrasonography adds essential information and should be a priority in the treatment of vascular adverse events.

In our referral center, which specializes in filler complications, more than 9 years of experience with ultrasonography used to detect fillers and their complications has led to its implementation for the emergency treatment of vascular adverse events. With high-frequency ultrasonography, the depth, location, and injectate size of all soft tissue fillers, including HA fillers, are visible and can be differentiated as to their composition.[21-24]

HA fillers are extremely hydrophilic (water binding) and, thus, are visualized on DUS as anechoic to hypoechoic lesions.[21,24-26] The injected HA depots are well defined. During breakdown, the characteristics of fillers may change, as can the appearance of fillers on ultrasonographs.[19] HA fillers have an anechoic appearance immediately after injection, which gradually changes to a more hypoechoic lesion over the ensuing months because the filler tends to integrate into the surrounding tissue over time. It may then by perceptible only as a hypoechoic to isoechoic structure, which is recognizable because it disturbs the normal architecture of its surroundings.

MATERIAL AND METHODS

Twenty-one patients from July 2018 through May 2019 were enrolled in this retrospective study. All were referred to the outpatient clinic of the Erasmus University Medical Center for vascular occlusion after HA injections in the face. Eligible patients were 18 years or older. Exclusion criteria included earlier use of permanent facial fillers, a vascular occlusion caused by a non-HA filler, pregnancy or intention of pregnancy, or the presence of an inflammatory condition of the face. Informed consent was obtained from all patients.

The location of intravascular injection, the time between onset of the vascular adverse event and treatment, and the amount of hyaluronidase units of treatment were recorded. Furthermore, complete recovery was noted when no obvious scarring was left after skin healing.

Upon arrival at our outpatient clinic, all patients had physical and DUS examination of the affected area. After this, the treating physician would attempt to inject 35 to 50 units of hyaluronidase into the obstructing intravascular bolus of filler under ultrasonographic guidance. Ancillary therapies used to increase blood flow were aspirin and the application

Abbreviations used:

DUS: duplex ultrasonography
HA: hyaluronic acid

of warm compresses. In the case of delayed referral in which disruption of skin integrity was visible or the presence of necrosis was evident, oral antibiotics were prescribed to prevent superinfection.

Immediately after an intravascular deposition, the freshly injected HA is detectable as a black (anechoic), well-defined lesion. With the DUS in duplex mode, blood vessels can be distinguished from the surrounding tissues because the blood flow is visible on the screen in pulsating red and blue colors. In normal vessels, laminar flow seen with DUS relates to successively higher velocities (a gradient) from zero at the walls to a maximum along the centerline of the vessel. Most filler obstructions are not truly 100% obstructive, varying from stenosis to nearly complete blockage. Both of these situations lead to disrupted laminar flow with marked turbulence. This turbulence is depicted as a combination of red and blue colors on DUS. Laminar flow recovers at some distance from the stenosis (Fig 1).

RESULTS

Twenty-one patients referred with a vascular adverse event due to HA fillers were treated with ultrasonographically guided hyaluronidase injections (Table II). Vascular occlusions were located at the lips (n = 8), nose (n = 4), forehead (n = 3), chin (n = 4), and cheek (n = 2). The involved arteries were the angular artery (n = 3), superior labial artery (n = 9), submental artery (n = 2), inferior labial artery (n = 2), columellar artery (n = 2), transverse facial artery (n = 1), superficial temporal artery (n = 1), supratrochlear artery (n = 3), and facial artery (n = 1).

Under ultrasonographic guidance, typically 35 to 50 units of HA (Hyalase "Dessau" 125 U/mL; Reimser Pharma, Greifswald, Germany) were injected (range, 35-150 U) into the HA deposits responsible for the occlusion (Table II), resulting in immediate restoration of blood flow (Fig 2). Clinical improvement of the livedo reticularis aspect of the skin was noted after blood flow was restored.

In 7 patients (3, 4, 9, and 18-21), a second treatment session was performed within 24 hours of the initial treatment. The blood flow had been restored with the first treatment; however, the second treatment was scheduled as a DUS checkup to clear some more defragmented HA pockets known to stimulate angiogenesis.[27,28] Two patients (3 and 9) with signs of developing necrosis before DUS-guided filler removal were advised to have hyperbaric oxygen therapy as well. In these cases, we are not sure whether restoring the blood flow alone would have been sufficient as a standalone treatment. Patient 4 who had a vascular injection leading to necrosis in the glabella area and the dorsum of the nose, had restored flow of the glabella area after initial hyaluronidase treatment. The following day, she developed some pustules over the dorsum of the nose; ultrasonographic application at this time showed another (sidetracked) pocket of HA, which was treated with HAse, with resultant clearing of the ischemic area of the nasal dorsum. The remaining vascular adverse events (except for patient 17) were resolved with 1 DUS-guided hyaluronidase injection (Figs 2 and 3). Patient 17 was referred for treatment, with a delay of 8 weeks. She described pain during injection in her chin, followed by pustules and necrosis. She had been treated with 1 injection of hyaluronidase directly after filler treatment and had recovered slowly with some scarring of her skin, but there was still a livedo aspect to the skin of her chin. With ultrasonography, a hypervascular aspect to the inferior labial artery was visualized, still surrounded by a hypoechoic, well-defined, homogeneous deposit of HA and decreased distal flow. Multiple collateral vessels were visible as well. Ultrasonographically guided injection of hyaluronidase cleared the persistent livedo aspect.

Figure 2 shows patient 4 before treatment, and Figure 3 shows the same patient 1 day after single treatment with ultrasonographically guided HAse injection.

DISCUSSION

Multiple hypotheses on the pathogenesis of filler-induced necrosis have been proposed, but the exact mechanism for tissue ischemia is not fully understood. Current theories include arterial or venous compression and intra-arterial injection leading to ischemia.[29]

The vascular compression theory holds that a large volume of filler injected into a tight space or scarred region, or as a consequence of intradermal bleeding or edema, may result in the occlusion of the vasculature and in subsequent ischemia.[30-33] However, clinical and histopathologic observations support the fact that the embolic consequence of intra-arterial filler injection is the cause of tissue ischemia and necrosis.[32-35] Nonetheless, the idea that the exact etiology of the ischemia is due to embolization of filler particles into the end arterioles has been disputed based on the fact that crosslinked HA gels exhibit high biological stability.[36-38] A further

Table I. Comparison of current hyaluronidase protocols and ultrasonographically guided hyaluronidase injections for intravascular hyaluronic acid events

Comparison of protocols	High-dose protocol	Ultrasonographically guided
Prior avoidance of vessels in high-risk areas by vascular mapping	No	Yes
Amount/extent of filler determined	No	Yes
Treatment timing	Immediate	Immediate
Dose interval	Hourly for 3-8 hours	Once
Hyaluronidase dose	High (>500 IU)	Low (35-50 IU)
Ancillary treatment	None	None
Treatment outcome	Very good (partial to full resolution)	Excellent (full resolution if performed early)
Special equipment necessary	No	High-frequency Doppler ultrasonography

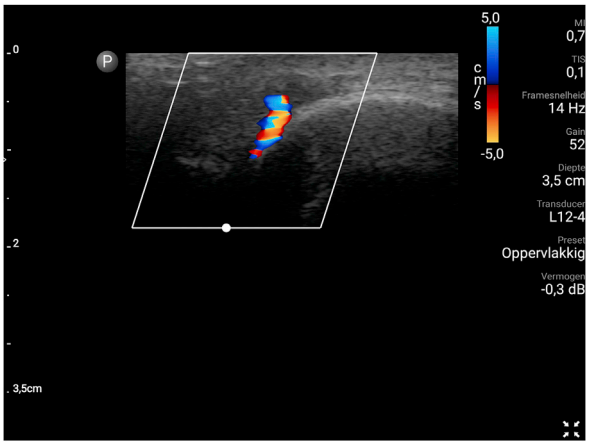

Fig 1. Hypervascular artery with hypoechoic pocket of hyaluronic acid filler.

participant in the occurrence of ischemia may be the phenomenon of arterial spasm.

The face has an extensive vascularity with numerous communicating branches between both direct and indirect linking vessels in the coronal, sagittal, and transverse planes.[39,40] These communicating branches consist of 2 quite distinct and different types of arteries. The first type of interconnections is less frequent and consists of vessels that are constant in caliber: the true anastomoses. The second and most common interconnections are formed by means of so-called choke vessels.[41-43] These anastomotic vessels have the functional ability to go into spasm, reducing their vessel caliber and, by this, controlling blood flow. It is thought that this additional protective mechanism will ensure vascular flow to the skin if needed but, on the other hand, will minimize flow to restrict necrosis in the event of damage. What triggers these vessels to go into spasm, whether it is critical perfusion pressure, oxygen tension, reaction to a toxin, or something else, is unknown.[42,43] Although well tolerated in skin, intravascular HA has been shown to be strongly irritant and potent in inducing a strong inflammatory response within the wall of blood vessels.[41] Thus, it is not improbable that an embolus of HA injected into an artery will lead to inflammation of the vessel wall. This has been postulated to induce spasm of the anastomotic connections around its anatomic perimeter to restrict necrosis, provided that these vessels are reduced-caliber choke anastomoses.[43,44]

The observations with DUS examination support this intra-arterial choke hypothesis. The arteries before the obstruction are hypervascular, with an absence of flow in the ischemic area, and most important, there is an immediate recovery of arterial flow after ultrasonographically guided hyaluronidase injection into the HA filler deposit. In the cases we have described, only the filler deposit causing the intravascular event was dissolved, followed in each case by a clinical improvement of the livedo aspect. This may imply that the compromising perfusion at the level of the capillary bed is the result of a filler deposit at the root of the bigger artery, leading to protective spasm of the choke anastomoses rather than arteriolar occlusion due to filler particles pushed through the capillary system. This would also explain the almost direct clearing of the livedo aspect once the filler deposit causing the vascular event is dissolved because the spasm will be neutralized.

However, if the connection by which the filler material is transported is a true anastomosis, without the possibility of reduction of caliber, the filler may get sidetracked into other branches of the vessel, leading to a second ischemic area.[43] Indeed, these sidetracked filler depots can be visualized with DUS examination (see patient nos. 4-6 in Table II). For

Table II. Patients and outcomes

Patient	Location	Artery	Units of hyaluronidase	Delay in treatment time	Number of treatments	Complete recovery
1	Nose	Angular artery	35	1 day	1	Yes
2	Nose	Angular artery	65	4 hours	1	Yes
3	Nose	Angular artery	35	1.5 days	2	Yes
4	Nose	Facial artery, superior labial artery	60/60	1 day	2	Yes
5	Lip	Superior labial artery, columellar artery	45/45	12 hours	1	Yes
6	Lip	Superior labial artery, columellar artery	40/40	3 hours	1	Yes
7	Lip	Superior labial artery	40	4 hours	1	Yes
8	Lip	Superior labial artery	50	3 days	1	Yes
9	Lip	Superior labial artery	40	1 day	2	Yes
10	Lip	Superior labial artery	40	1 day		
11	Forehead	Supratrochlear artery	35	4 hours	1	Yes
12	Forehead	Supratrochlear artery	35	8 hours	1	Yes
13	Forehead	Supratrochlear artery	150	2.5 days	1	Yes
14	Chin	Submental artery	50	4 days	1	Yes
15	Chin	Submental artery	75	1 day	1	Yes
16	Chin	Inferior labial artery	60	1.5 days	1	Yes
17	Chin	Inferior labial artery	50	8 weeks	1	No
18	Parietal area	Superficial temporal artery	75/50	3 weeks	2	
19	Lip	Superior labial artery, columellar artery	45/45	3 days	2	Yes
20	Mandibula	Transverse facial artery	80/50	3 days	2	Yes
21	Lip	Superior labial artery, columellar artery	40/40	3 days	2	Yes

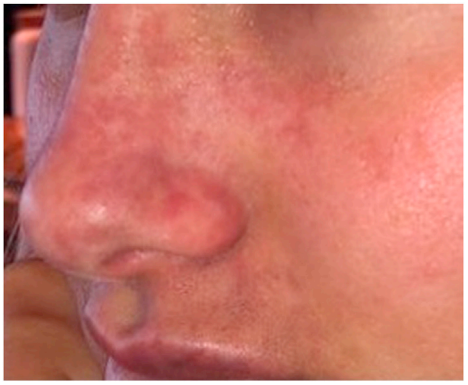

Fig 2. ■■■.

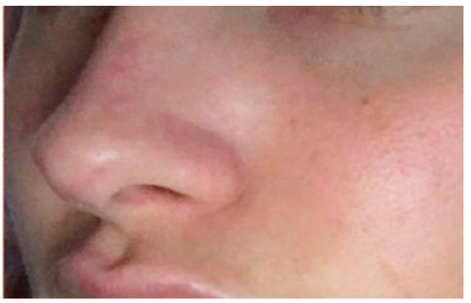

Fig 3. ■■■.

example, during a vascular adverse event, filler material was found both in the superior labial artery and further away in the columellar artery. Undoubtedly, the use of DUS is a valuable source of critical information on vascular adverse events; however, more extensive research in this area, as in the case of ocular vascular events,[45] is warranted.

The chemical composition and physical properties of HA fillers differ by HA concentration, amount of crosslinking, particle size, extrusion force, and elastic modulus. Thus, the available hyaluronidases have variable interactions in a time- and dose-dependent manner.[41] Differences in the sensitivities of specific fillers to enzymatic degradation seem to affect tissue residence time and the speed at which the product is dissolved.[46,47] To overcome this issue in urgent cases of intravascular occlusion, higher doses of hyaluronidase are recommended to compensate for possible relative resistance of the gel to degradation.[46-50] However, with ultrasonographically guided injection of hyaluronidase, an average injected dose of 35 to 60 units per deposit was sufficient in most cases, independent of the type of HA filler used. A possible explanation may be that precise injection into the targeted HA deposit requires fewer units.

As in all fields of therapeutic medicine, the development of initiatives to ensure safety in the aesthetic arena is paramount for optimal patient outcomes. The use of DUS for facial arterial mapping, safe deployment of HA, and directed low-dose

hyalruonidase reversal of impending intravascular adverse events is a welcome technological advancement. Although training in the use of ultrasonography and its interpretation is required, the learning curve is rapid, and ongoing practice is necessary. Because the use of DUS adds extra essential information, it is our opinion that this modality will inevitably become mainstream as an integral part of the prevention and treatment of injection adverse events.

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