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

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Abstract

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 an vascular adverse event safety of hyaluronic acid filler treatments

Methods: duplex / ultrasound is used to detect the hyaluronic acid filler causing the intra-arterial obstruction

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

Conclusion: As the use of duplex / ultrasound adds extra essential information, its use may become an integral part of the prevention and treatment of injection adverse events.

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

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Introduction

The popularity of robust hyaluronic acid (HA) fillers for facial contouring has seen a dramatic rise in the past years leading to their dominance in the aesthetic marketplace[1]. The hyaluronic acid molecule itself is a high–molecular weight polysaccharide, which, at physiologic pH, binds water extensively, is completely resorbable., and therefore biochemically considered to be a safe compound[2,3]. However, even with safe degradable products, the techniques and treatment protocols employed by physicians must portend a low rate of adverse events. The Department of Dermatology, Erasmus Medical Centre, Rotterdam has established an out-patient 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 and accumulation of product (due to underlying muscle movement), and vascular events [4,5,6,7]. The frequency seen at the clinic of intravascular complications leading to skin necrosis or blindness is as of this publication (April 2019) noted to be twice monthly . An increasing number of articles and guidelines have recently been published regarding these disastrous complications, including a safety warning of the FDA on its website in 2015 [,4,,7,8,9,10,11].

One of the advantages of HA fillers is their dissolvability with hyaluronidase in the event of post-injection 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 an allergic reaction as the most serious complication occurring at an incidence of 1:2000[14].

For a vascular adverse event leading to skin necrosis, the use of hyaluronidase (HAse) 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 [16,17,18]. Therefore, the current leading guideline involves the use of pulsed high-dose hyaluronidase in one hour intervals in order 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 x 3 cms, a minimum of 500 iu of hyaluronidase is advised. It has also been recommended to keep the patient in the clinic for observation between pulses for anywhere from three to eight treatment sessions until normal skin color returns[18].

The outcome from this high dose protocol has shown to be very effective, as 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 as well as the amount of filler is neither detectable nor appreciated. The hourly, multiple pulsed injections of high dose hyaluronidase over the ensuing hours has intendant skin trauma, is arduous, and often leads to exhaustion of both the patient and the physician abandoning the treatment until the subsequent 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.

It is with this understanding, that the use of a duplex/ultrasound (DUS) device was investigated for vascular mapping in high risk zones pre-injection, as well as to determine both quantity and location of the HA to guide treatment in those cases of vascular compromise[20]. A comparison of current hyaluronidase protocols and ultrasound-guided therapy is listed in Table 1.

(Table 1)

In our referral centre specialized in filler complications, the nine year plus experience with ultrasound in detecting fillers and their complications has evolved to its implementation for the emergency treatment of vascular adverse events. With high frequency ultrasound, the depth,

location and injectate size of all soft tissue fillers including hyaluronic acid fillers are visible and can be differentiated as to their composition[21,22,23,24].

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

Material and methods

Twenty one patients from July 2018 to May 2019 were enrolled in this retrospective study. All were referred to the out-patients clinic of the Erasmus University Medical Centre for vascular occlusion after hyaluronic acid 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 intent for 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 vascular adverse event and treatment, the amount of HAse units of treatment were recorded. Furthermore, complete recovery was labeled as positive when no obvious scarring was left after skin healing.

Upon arrival at our out-patient clinic, all patients underwent physical and DUS examination of the affected area. After this the treating physician would attempt to inject 35-50 units of hyaluronidase into the obstructing intravascular bolus of filler under ultrasound guidance. Ancillary therapy instituted to increase blood flow were aspirin (ASA) and the application of warm compresses. In those cases of delayed referrals where 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 hyaluronic acid is detectable as a black (anechoic) well defined lesion. With the DUS in duplex mode, blood vessels can be distinguished from the surrounding tissues as the blood flow is visible on the screen in pulsating red and blue colors. In normal vessels, laminar flow as seen with duplex ultrasound 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 near 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 colours on the duplex ultrasound. Laminar flow recovers at some distance from the stenosis. (figure 1).

(Figure 1)

Results

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

Under ultrasound guidance, typically 35-50 units of hyaluronidase (Hyalase, 125 units per 1 ml) were injected (minimum of 35 units and a maximum of 150 units).into the hyaluronic acid deposits responsible for the occlusion (Table 2), resulting in immediate restoration of blood flow (figure 3 c, 3d). Clinical improvement of the livedo reticularis aspect of the skin was noted after restoring the blood flow.

(Table 2)

In seven patients (3,4, 9, 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 an DUS checkup to clear some more defragmented hyaluronic acid pockets known to stimulate angiogenesis [27]. Two patients (3 and 9) with signs of developing necrosis before DUS guided filler removal were advised to get 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 with 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 her nose; ultrasound application at this time revealed 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 one DUS-

guided hyaluronidase injection (figure 2,3). 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 one 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 ultrasound, a hypervascular aspect to the inferior labial artery was visualized, still surrounded by a hypoechoic well-defined homogeneous deposit of hyaluronic acid and decreased distal flow. Multiple collaterals were visible as well. Ultrasound guided injection of hyaluronidase cleared the persistent livedo aspect.

(Figure 2, 3)

Patient No. 4 before (figure 2) treatment and one day following (figure 3) single treatment with ultrasound-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 occlusion of the vasculature and in subsequent ischemia[30,31,32]. However, clinical and histopathologic observations support the fact that the embolic consequence of intra-arterial filler injection is the culprit in causing tissue ischemia and necrosis[31-,34] . The exact etiology of the ischemia being due to embolization of filler particles into the end arterioles none-the-less has been disputed based on the fact that crosslinked HA gels exhibit high bio stability [35, 36,37]. A further participant in the occurrence of ischemia may be the phenomenon of arterial spasm.

The face has a very extensive vascularity with numerous communicating branches between both direct and indirect linking vessels in the coronal, sagittal, and transverse planes[38,39]. These communicating branches consist of two 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[40,42]. 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 anything else, is unknown[41,42]. Although well tolerated in skin, intravascular hyaluronic acid has shown to be strongly irritant and to be very potent in inducing a strong inflammatory response within the wall of blood vessels[40]. Thus, it is not improbable that an embolus of hyaluronic acid 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 anatomical perimeter in order to restrict necrosis, provided that these vessels are reduced-caliber choke anastomoses[42].

The observations with DUS examination supports 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 ultrasound guided hyaluronidase injection into the HA filler deposit. In our cases studied above, 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 livedo aspect once the filler deposit causing the vascular event is dissolved, as 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[42]. Indeed, with DUS examination these sidetracked filler depots can be visualized (No 4,5,6 table 2). For 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[44], is definitely warranted.

The chemical composition and physical properties of HA fillers differ by HA concentration, amount of cross-linking, particle size, extrusion force, and elastic modulus. Thus, the available hyaluronidases have variable interactions in a time and dose dependent manner[40]. Differences in sensitivity of specific pfillers to enzymatic degradation seem to affect tissue residence time and the speed at which the product is dissolved[,45,46] . 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 [45 - 49]. However, with ultrasound-guided injection of hyaluronidase, an average injected dose of 35-60 units per deposit was sufficient in most cases, independent of the type of HA filler used. A possible explanation may be the precise

injection into the targeted HA deposit requiring a lower amount of 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 hyaluronic acid and directed low-dose hyalruonidase reversal of impending intravascular adverse events is a welkom technological advancement. Although training in the use of ultrasound and its interpretation is required, the learning curve is rapid and ongoing practice is necessary. As the use of DUS adds extra essential information, it is the authors' 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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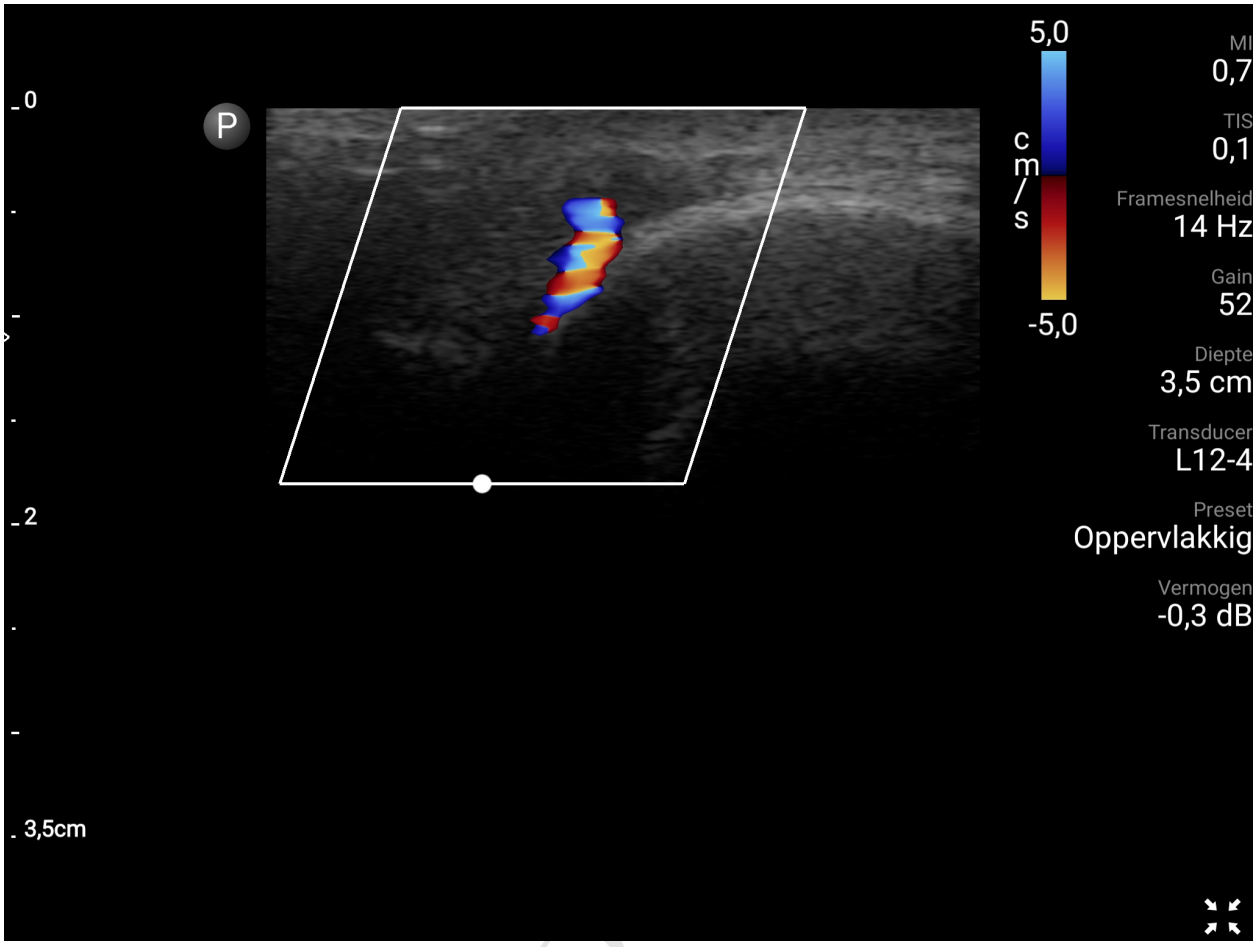
Table 1. Comparison of Current HAse Protocols and Ultrasound-Guided HAse Injections for Intravascular HA Events

	High dose protocol	**Ultrasound 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 (>500iu)	Low (35-50iu)
Ancillary Tx	None	None
Treatment Outcome	Very Good (partial to full resolution)	Excellent (full resolution if performed early)
Special equipment necessary	No	High frequency Doppler US

Table 2. Patients and Outcomes

	Location	Artery	Units of HAse	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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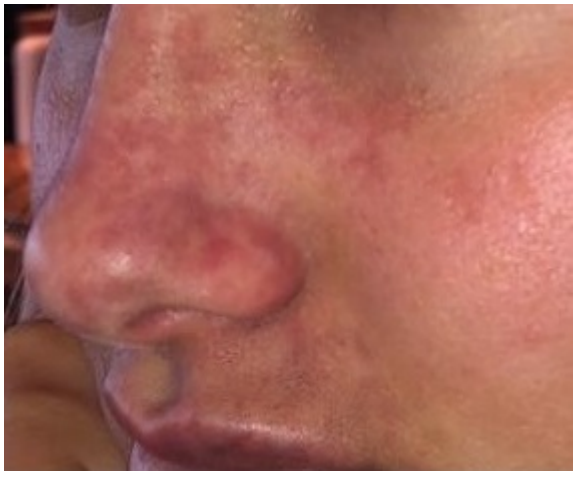

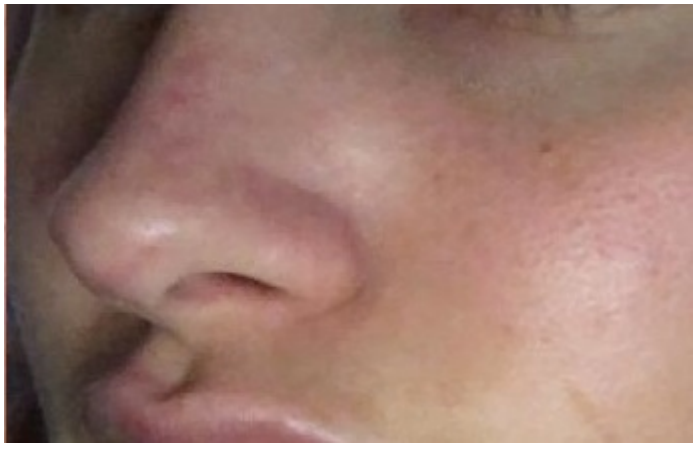

Capsule summary

- 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
- The use of duplex / ultrasound adds essential information and should be a priority in the treatment of vascular adverse events