Ultrasound-Guided Targeted vs Regional Flooding: A Comparative Study for Improving the Clinical Outcome in Soft Tissue Filler Vascular Adverse Event Management

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Abstract

Background: Adverse vascular event management following hyaluronic acid–based aesthetic injections relies on the administration of hyaluronidase which is capable of enzymatically degrading the injected product and improving clinical symptoms. Two protocols are currently available to manage such complications: "ultrasound-guided targeted" and "flooding".

Objectives: The aim of this study was to compare the 2 protocols in terms of the volume of hyaluronidase utilized, and the onset and degree of clinical improvement.

Methods: A comparative case series of 39 patients was retrospectively evaluated. The patients were initially treated with the "flooding" protocol and then treated with the "ultrasound-guided targeted" protocol due to no or little improvement.

Results: The "ultrasound-guided targeted" protocol utilized a mean [standard deviation] total of 122.5 [34] IU of hyaluronidase, whereas the "flooding" protocol utilized 1519.4 [1137] IU, which represents a statistically significant reduced amount of injected hyaluronidase ($P = 0.028$). There was no clinical improvement in 92.3% and only little improvement in 7.7% of the treated patients following the first applied "flooding" protocol, but there was a 100% immediate improvement when subsequently treated with the "ultrasound-guided targeted" protocol. Ultrasound imaging revealed that the application of hyaluronidase restored normal blood flow both in the perivascular space and in the superficially located subdermal soft tissues.

Conclusions: Despite its limitations in study design, this retrospectively evaluated case series revealed that the "ultrasound-guided targeted" protocol utilized less hyaluronidase and restored clinically visible symptoms faster. The effect of this protocol is best explained by the perforasome concept which will need to be investigated further in future studies.

Level of Evidence: 4

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The demand for minimally invasive procedures is constantly increasing despite the effects of the COVID-19 pandemic and the global economy. According to the statistics annually released by The Aesthetic Society, the number of soft tissue filler injections performed in 2021 in the United States was 1,857,339, which represents a 42% increase compared with 2020 (1,304,645).[1] This positive trend has unfortunately been accompanied by an increase in adverse events,[2,3] and a recent survey-based study revealed that 28.6% (n = 106) of 370 participating dermatologists reported to have had at least 1 vascular occlusion event in the past.[4] It is most likely that the real number of vascular adverse events is higher among injectors because some events might not be reported in the scientific literature.

Currently accepted pathologic mechanisms behind vascular adverse events following soft tissue filler injections are based on the assumption that the injected material is either applied intra-arterially and causes a mechanical (from the filler material itself) and thrombotic (from a formed blood clot) embolus[5,6] or that the injected material is compressing an artery;[7,8] both mechanisms result in a compromised blood supply to the consecutive perfused facial regions.

The treatment of choice for adverse vascular events is the administration of hyaluronidase, which can enzymatically break down hyaluronic acid–based soft tissue fillers within the facial soft tissues. The accepted standard protocol for the management of such adverse events is the 2017 "High Dose Pulsed Hyaluronidase Protocol" by DeLorenzi in which the application of 500 IU per small area and 1500 IU for larger areas was recommended. The author also suggested: "We need to wet the entire volume of ischemic tissue with [hyaluronidase], because we need to hydrolyze the filler throughout the entire block of tissue," which resulted in the procedure of "flooding" the affected tissue with hyaluronidase.[9] The affected tissue is assumed to be the tissue area in which skin symptoms are clinically visible. In 2019, Schelke et al reported that ultrasound-guided and targeted injections of 35 to 150 IU hyaluronidase for hyaluronic acid–based soft tissue filler complications can prevent skin necrosis, starting a paradigm shift in how best to treat adverse vascular events: "ultrasound-guided targeted injections" or the "flooding" procedure.[10]

Due to the unpredictable, highly variable, and urgent nature of the occurrence of adverse vascular events, no ethically compliant study can be performed to test the clinical outcome in a direct comparative study design. Therefore, a different approach was selected for the purposes of this retrospective data analysis. The clinical outcome of the initially performed "flooding" procedure was compared to the clinical outcome of "ultrasound-guided targeted" hyaluronidase injections in the same patients. It is hoped to provide guidance for practitioners on how to best manage adverse vascular events following hyaluronic acid–based soft tissue filler injections.

METHODS

Study Design

The data analyzed in this study were retrospectively evaluated from consecutive patient records of the first (L.W.S.) and second author (P.J.V.) based on their clinical work at the Department of Dermatology, Erasmus Medical Center, Rotterdam, the Netherlands and at a private practice in Amsterdam, the Netherlands. All patients included in this retrospective analysis were initially treated for various facial aesthetic indications at external clinics, resulting (unfortunately) in adverse vascular events. All patients were treated by their external injector with hyaluronidase following the "flooding" procedure without clinical improvement. All referring injectors were physicians and trained in the high-dose pulsed protocol published by de Lorenzi.[9] This protocol is the accepted standard of care in the Netherlands and great emphasis is placed on its education by the Dutch Society of Cosmetic Medicine. The protocol, however, was executed in this study in 100% of the cases with a cannula instead of a needle as initially published.[9] This alteration is based on a previous publication by Pavicic et al, which identified that product spread is larger with a cannula than with a needle which might be beneficial for distributing hyaluronidase across the facial soft tissues during the treatment.[11] In 14 of the referred cases, physicians had a practicing experience of 0 to 5 years, in another 14 cases, 5 to 10 years, in 7 cases, 10 to 15 years, and in 2 cases, 20 to 25 years; in the remaining 2 cases this information was not available.

The referring physician had to complete a transfer sheet with detailed demographic and treatment-related information. The brand of soft tissue filler utilized was not requested on the transfer sheet, only the type of material administered: hyaluronic acid, calcium hydroxyl apatite, silicone, others; in this study 100% of the injected material was hyaluronic acid–based filler material. The reasoning behind not requesting information about the brand of injected soft tissue filler is based on the authors' previous experience which has shown that despite the different rheologic properties of the various facial fillers (cohesivity, hyaluronic acid concentration, elastic modulus, water binding capaticity, etc) the outcome of adverse event management was carried out independently and results did not differ among the different brands of hyaluronic acid–based soft tissue fillers.

After transferral of the patients to the clinics of the authors of this study, they were treated following previously published ultrasound-guided and targeted treatment protocols for adverse event management of vascular

complications.[10] The comparison of the outcome between the 2 treatment protocols, including the amount of hyaluronidase utilized and the change in clinical symptoms with time, is the subject of this study.

All patients included in this study provided written informed consent for accessing their charts and extracting their data for the purposes of this study. No charts were accessed if patients declined to participate in this study. The observational period for this study was May 2018 to January 2022.

All treatments were performed in adherence with the Declaration of Helsinki and in accordance with the standards of good clinical care following local guidelines and regulations. The study did not require ethics committee approval because ultrasound imaging is considered standard of care for the management of adverse vascular events according to the Medical Research Involving Human Subjects Act.[10]

Statistical Analysis

Descriptive and comparative analyses were conducted with SPSS Statistics 23 (IBM, Armonk, NY) and results were considered statistically significant at a probability level of ≤ 0.05 to guide conclusions. Values are presented as mean value and the respective 1× standard deviation (SD) accompanied by the data range: mean [SD] (range).

RESULTS

Patient Demographic Data

Of the 39 patients included in this retrospective data analysis, 36 (92.3%) were females and 3 (7.7%) were males, with a mean age of 35.3 [11.8] years (range, 18-58 years) and with the following Fitzpatrick skin type distribution: Type I, 18 (46.2%); Type II, 14 (35.9%); and Type III, 7 (17.9%).

Initial Aesthetic Treatment

Patients were treated for facial volumizing, contouring, repositioning, and reshaping, of which the upper lip and the nose (both n = 7; 17.9%) were most frequently targeted, followed by the chin and the midface (both n = 6; 15.4%) and the nasolabial fold (n = 4; 10.3%). A needle was used in 24 (61.5%) treatments, whereas a cannula (sizes unknown) was used in 15 (38.5%). A bolus injection technique was performed in 20 (51.3%) of the cases, whereas a fanning technique was performed in 19 (48.7%) of the treatments. The product was administered in 19 (48.7%) treatments in contact with the periosteum, in 12 (30.8%) treatments into the subcutaneous plane (unspecified), and in 8 (20.5%) treatments subdermally. The average amount of filler material injected was 0.33 [0.2] mL (range, 0.05-1.0 mL). For details, see Table 1.

Table 1. Demographic Data and Background Information on the Injection Technique Utilized During the Initial Aesthetic Treatment

	n	*(%)*
Number of patients (total)	39	
Females	36	92.3%
Males	3	7.7%
Fitzpatrick Type I	18	46.2%
Fitzpatrick Type II	14	35.9%
Fitzpatrick Type III	7	17.9%
Needle used for treatment	24	61.5%
Cannula used for treatment	15	38.5%
Bolus injection technique	20	51.3%
Fanning injection technique	19	48,.7%
Injection in contact with periosteum	19	48.7%
Injection into subcutaneous plane	12	30.8%
Injection into subdermal plane	8	20.5%
Average amount of filler (mL)	0.33	

Presentation of Adverse Events

In 38 (97.4%) cases, the onset of clinical symptoms of the adverse event was immediate; in the remaining case (n = 1; 2.6%) the symptoms started within the next few hours. The most frequent clinical symptom initially observed was erythema, followed by pain, livedo reticularis, edema, blanching, and hematoma, presenting in this order. Table 2 shows a cross-tabulation between the injection location and the type of clinical symptoms. In 33 (84.6%) cases, the skin symptoms presented in the same location as the injection was performed, whereas in 6 (15.4%) cases, the skin symptoms surfaced in an adjacent area: injections of the nose presented in the glabella, injections of the nasolabial fold presented in the nose, injections of the upper lip presented in the nasolabial fold and midface. For details, see Table 3.

Treatment Following the "Flooding" Protocol

The interval between symptom onset and adverse event management utilizing hyaluronidase with the "flooding"

Table 2. Area of Injection and the Type of Adverse Event Observed

Area injected	Erythema	Blanching	Edema	Livido reticularis	Pustula	Pain	Itching	Hematoma
Chin	5	2	2	3	1	3	—	—
Upper lip	4	5	1	4	1	2	—	—
Nose	6	1	2	3	1	2	—	—
Nasolabial fold	4	1	3	1	—	1	—	—
Temple	—	—	—	—	—	1	1	—
Lower lip	2	—	2	1	—	2	—	—
Lateral cheek	1	—	—	1	—	1	—	—
Corner of the mouth	1	1	—	—	—	1	—	—
Midface	4	—	1	2	—	2	—	1
Forehead	—	1	—	—	—	1	—	—
Jawline	1	—	—	1	—	1	—	—

Numbers represent the count.

Table 3. Cross-Tabulation Between the Injected Facial Region and the Region of the Observed Skin Symptoms

	Chin	Upper lip	Nose	Nasolabial fold	Temple	Lower lip	Corner of the mouth	Midface	Forehead	Jawline	Glabella
Chin	6	—	—	—	—	—	—	—	—	—	—
Upper lip	—	5	—	1	—	—	—	1	—	—	—
Nose	—	—	6	—	—	—	—	—	—	—	1
Nasolabial fold	—	—	1	3	—	—	—	—	—	—	—
Temple	—	—	—	—	1	—	—	—	—	—	—
Lower lip	—	2	—	—	—	1	—	—	—	—	—
Lateral cheek	—	—	—	—	—	—	—	1	—	—	—
Corner of the mouth	—	1	—	—	—	—	1	—	—	—	—
Midface	—	—	—	1	—	—	—	5	—	—	—
Forehead	—	—	—	—	—	—	—	—	1	—	—
Jawline	—	—	—	—	—	—	—	—	—	1	—

protocol was immediate in 24 (61.5%) cases, but in the remainder of the cases ranged between 1 hour and 6 days. Once the treatment was initiated, an average of 1519 [1138] IU (range, 30-4500 IU) of hyaluronidase (Hyason, Organon, the Netherlands) was administered exclusively, and in 14 (35.9%) cases, corticosteroids (oral), acetylsalicylic acid (oral), warm compresses, and manual massage were administered in addition to the hyaluronidase. The hyaluronidase was mixed with 0.9% lidocaine (in 9 out of 10 cases; mixed with saline in the remainder of the cases) and distributed superficially within the affected facial regions utilizing a cannula fanning technique. Following this treatment, "little" improvement of the initial symptoms was observed in only 3 (7.7%) cases, whereas in the remainder of the cases (n = 36; 92.3%) no improvement was reported.

Treatment Following the Ultrasound-Guided Targeted Protocol

Due to little to no improvement in the patient symptoms being observed, patients were referred to the authors' clinic

and a different treatment protocol was initiated. The interval between the initial aesthetic injection and the beginning of the new protocol treatment ranged between 4 hours to 8 weeks with an average value of 4.4 [9.4] days (range, 0-56 days). Following ultrasound assessment, guided injections were performed targeting the main arterial branch of the supplying artery and not the overlying soft tissues where the skin symptoms were visible.

In all cases (100%), Doppler ultrasound (18 MHz linear transducer, Affinity 70; Philips, Eindhoven, the Netherlands) revealed hypervascularity around the main arterial trunk and an anechoic or hypoechoic oval mass adjacent to or surrounding that respective vessel which would correspond to the initially administered soft tissue filler material (Figures 1, 2). The overlying soft tissues where the redness, pain, livedo reticularis, edema, blanching, and hematoma were observed displayed a reduced vascularization with little to no vascular signal during Doppler ultrasound imaging. No soft tissue filler material was identified within the superficial soft tissue facial regions which revealed areas of hypovascularity during Doppler ultrasound assessment.

Once the arterial trunk and the filler material were identified during ultrasound imaging, an mean of 95 [65] IU (range, 25-400 IU) of hyaluronidase was injected with a needle targeting the perivascular space. In 6 (15.4%) patients, a second dose of hyaluronidase was injected the next day (24 hours later), similarly utilizing Doppler ultrasound imaging to guide the procedure; in those patients an average of 51 [10] IU (range, 40-65 IU) of hyaluronidase was injected as the second dose. The decision to apply a second dose was based on the absence of immediate clinical and ultrasonographic improvement after the first treatment.

Outcome Following the Ultrasound-Guided Targeted Protocol

The application of hyaluronidase was performed under direct ultrasound guidance at the base of the main arterial trunk and not within the superficially located soft tissues which displayed the clinically visible skin symptoms. The reduction of the hypervascularity at the base of the arterial trunk and the concomitant hypovascularity at the superficially located soft tissues occurred immediately, within less than 60 seconds, after the administration of the hyaluronidase. Once the blood flow was restored, as assessed by ultrasound, the clinical symptoms, including livedo reticularis and pain, similarly resolved immediately (except in cases of hematoma, which remained) in 100% of the treated 39 patients. The most prominent visible signs of clinical improvement were the reduction in erythema and livedo reticularis. The slightly more deeply located blueish discoloration likewise reduced, which immediately changed the overall tissue impression of the affected area.

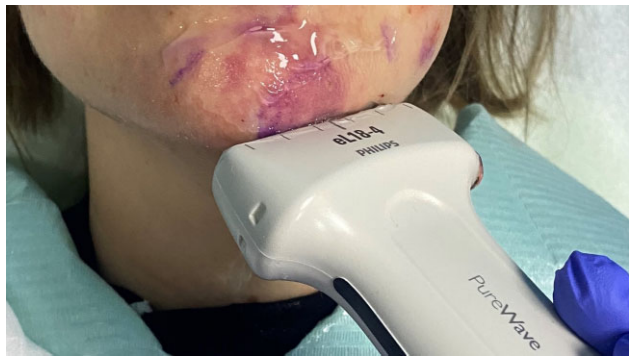

Figure 1. Photograph of a 35-year-old female study participant showing the ultrasound imaging of the mental and perioral region where a skin redness and livedo as vascular adverse events can be seen.

In cases of resulting skin lesions, a skincare regimen was initiated and followed up according to the standard of care at the treating clinic. Fucidin 20 mg/g ointment was applied if crusting and skin necrosis occurred. In case of persistent erythema after skin necrosis, intense pulse light therapy was advised. Depending on the immediate results of ultrasound imaging, clinical assessment, and clinical presentation (such as severity of scabs or pustule formation), a follow-up visit was scheduled with the patient the next day or their condition was checked remotely by virtual video contact or telephone. All patients included in this retrospective analysis (n = 39, 100%) recovered without scars, skin discolorations, or any functional deficits (Figures 3-6).

DISCUSSION

In this retrospective evaluation of a case series, consisting of 39 treated patients, we describe an alternative treatment protocol for adverse vascular events following facial soft tissue filler injections utilizing hyaluronic acid–based materials. This treatment protocol was initially described in 2019[10] and has been continuously applied by the authors in their treatment regimen for adverse vascular events. We designed and conducted this study to present and evaluate this ultrasound-guided and targeted approach. The comparative study design might allow for a direct comparison between the previously published "High Dose Pulsed Hyaluronidase Protocol" by DeLorenzi[9] and the ultrasound-guided targeted protocol by Schelke et al.[10] The goal of this study was not to question the effectiveness or feasibility of the already established and widely accepted high-dose pulsed protocol, which floods the affected soft tissue area with hyaluronidase. The objective was rather to explore an alternative possibility for treating adverse vascular events for those who can utilize ultrasound imaging in specific patient cases.

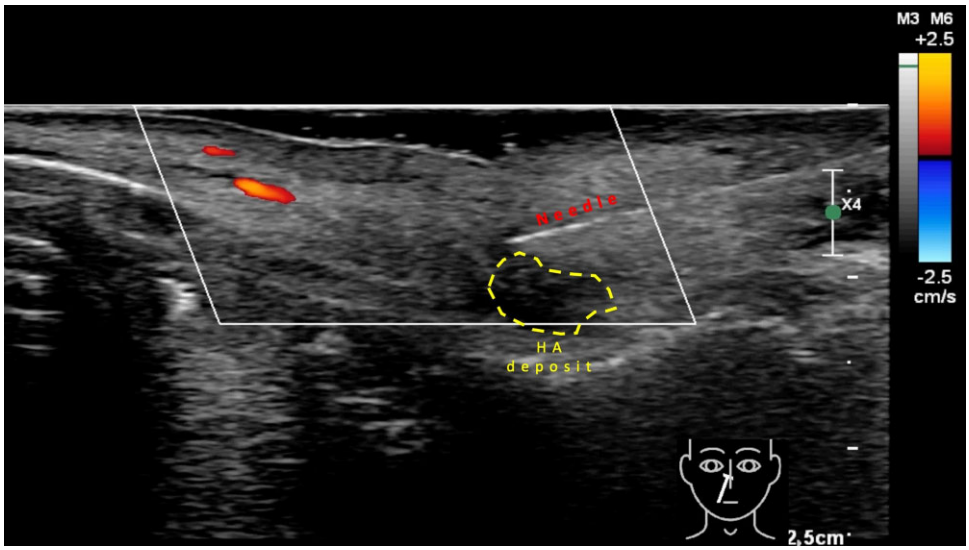

Figure 2. Ultrasound image of a 36-year-old female study participant showing the needle injection of hyaluronidase into a hypoechoic area which resembles the previously injected hyaluronic acid causing the vascular adverse event. The blood flow is restricted.

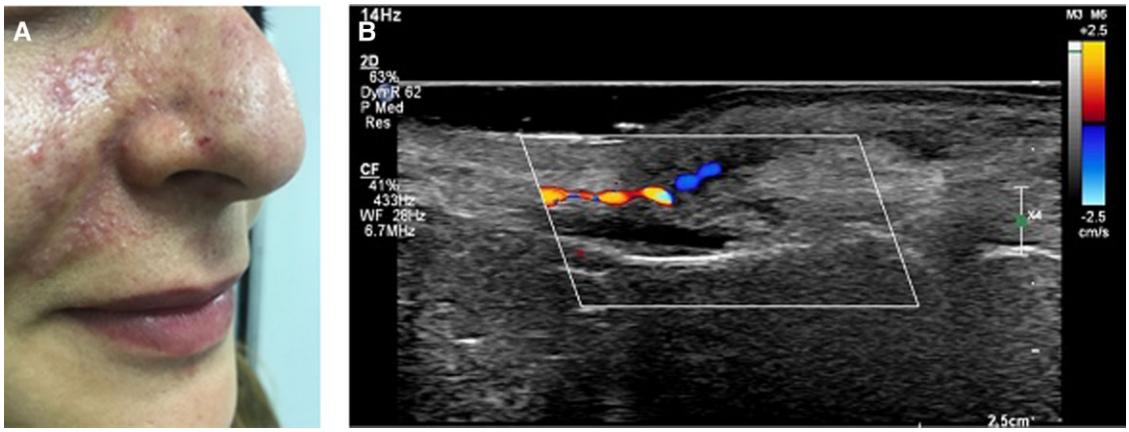

Figure 3. (A) Photograph of a 36-year-old female study participant with skin lesions in the nasolabial fold as a result of restricted blood flow caused by vascular occlusion. (B) Doppler ultrasound image of the nasolabial fold showing the restricted blood flow.

The comparative study design has its weaknesses as it can be argued that the observed clinical improvement was established by the first treatment session utilizing the "flooding" protocol, and the "ultrasound-guided targeted" protocol is piggybacking on the success of the first treatment without adding any effectiveness of its own. When comparing the clinical outcome, it can be stated that there was no clinical improvement in 92.3% and only little improvement in 7.7% of the treated patients following the first applied "flooding" protocol. In addition, ultrasound imaging revealed that facial blood flow was still affected in 100% of the treated patients with hyper- and hypovascular areas in the deep and superficial fascial layers, respectively. Therefore, it can be assumed that no additive effect was present but rather a sequential event took place with similar baseline status for both protocols as the same patients with the same metabolism and demographics were treated similarly to a longitudinal interventional study design. Further, the clinical improvement was visible only after the "ultrasound-guided targeted" protocol was applied, which was confirmed with Doppler ultrasound imaging as normal blood flow was restored and the filler material was dissolved; no anechoic or hypoechoic material surrounding the main arterial trunk was visible.

The "ultrasound-guided targeted" protocol utilized a total (both sessions combined) of 123 [34] IU, whereas the "flooding" protocol utilized 1519.4 [1137] IU, which represents a statistically significant reduced amount of injected

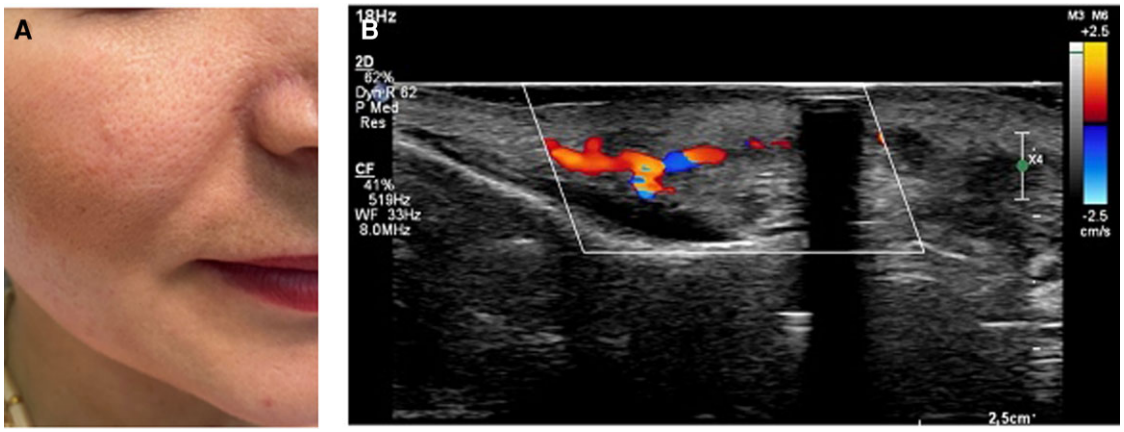

Figure 4. (A) Photograph of a 36-year-old female study participant with clinical improvement of the nasolabial fold in an 8-week follow-up examination. (B) Doppler ultrasound image of the nasolabial fold showing a significantly improved blood flow.

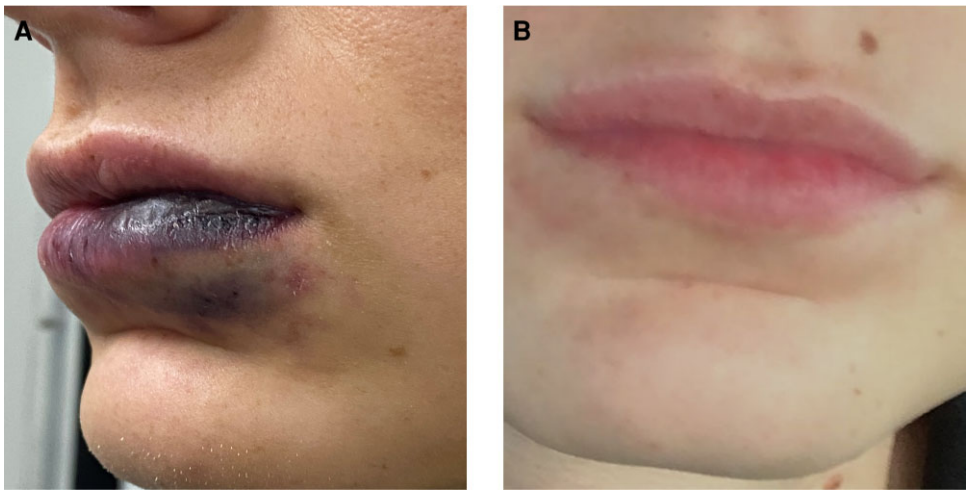

Figure 5. (A) Photograph of an 18-year-old male study participant showing the clinical picture after a vascular adverse event in the lower lip and (B) a photograph after 1 week showing significant clinical improvement after the ultrasound-guided targeted hyaluronidase injection protocol.

hyaluronidase ($P = 0.028$). The observed range of 25 to 400 IU resulted from the immediate effect following the performed hyaluronidase injections which were directly inspected under ultrasound guidance, which sometimes needed less (25 mL) and sometimes more (400 mL) volume per procedure depending on the injected volume and on the hyaluronidase diffusion and effect. Hyaluronidase is an endoglycosidase that breaks down glycosaminoglycans, which are a major component of the extracellular matrix of the body, and has been shown to cause urticaria and angioedema in certain cases.[12–14] Reduced amounts of administered hyaluronidase might be better tolerable for the facial soft tissues because the risk for allergic reactions is reduced and the extracellular matrix is not attacked and dissolved, potentially resulting in more aesthetic deficiencies for the patient.

The authors are aware of the difficulties of utilizing ultrasound imaging for such procedures, which include the purchase of an appropriate device (the cost of which can range from US$5000 to US$100,000), and the learning curve, reproducibility, and thus reliability of the method itself, as well as the applied anatomic knowledge required to translate the black-and-white images into a meaningful representation of the underlying facial soft tissues.[15–17] Therefore, the presented protocol might not be useful for every user but might offer benefits for those with the appropriate device and specialized training. Novice injectors, in particular, might find it difficult to refuse the demands of their patients because of pressure to perform, or due to financial reasons, or due to social media pressure; they might be forced into situations that are difficult to navigate when it comes to preventing adverse events. Experienced injectors, on the

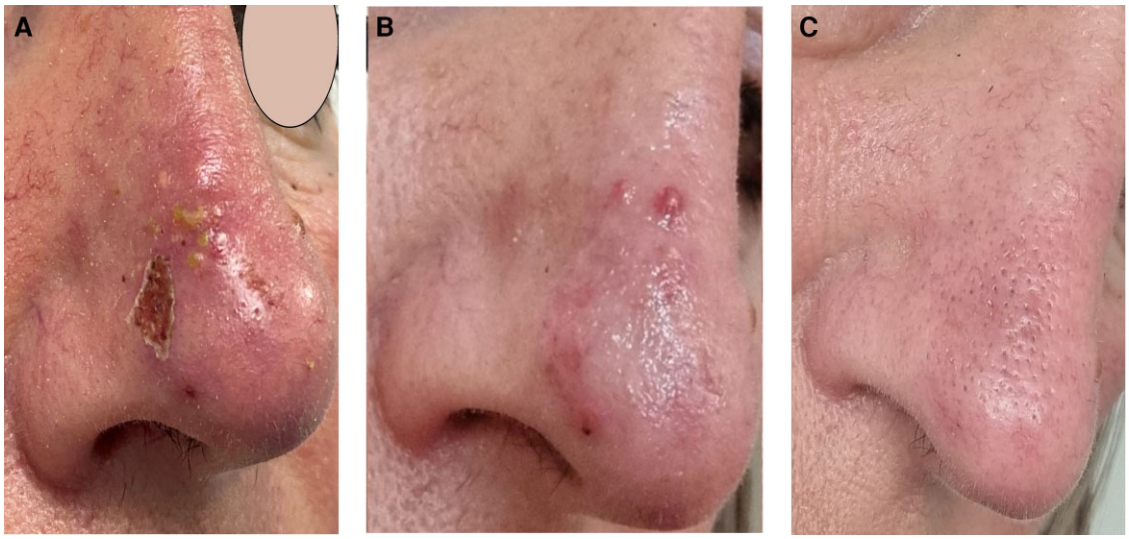

Figure 6. (A) Photograph of a 41-year-old female study participant showing the clinical picture after a vascular adverse event of the nose before treatment, (B) a photograph showing the clinical picture after a vascular adverse event of the nose 3 days after treatment, and (C) a photograph showing significant clinical improvement after a vascular adverse event of the nose 2 weeks after treatment.

contrary, may have the funds and the ability to say no but also might have different opportunities to learn and to evolve along with new technologies (ultrasound) which help them either to manage better or to prevent adverse events. This unfortunately points to an unfair imbalance when it comes to utilizing ultrasound technology and to understanding and preventing adverse events in the aesthetic field. Nevertheless, this study was designed to show an alternative pathway in a comparative study design and to open possibilities for implementing ultrasound imaging more deeply in aesthetic practice.

It is unclear why the effects observed occur immediately after the "ultrasound-guided targeted" protocol but were not clinically visible after the "flooding" protocol was applied. One reason could be that the hyaluronidase was applied in the incorrect anatomic location to counteract the clinical symptoms. The fact that almost all clinical symptoms, including erythema, pain, livedo reticularis, edema, and blanching, improved almost immediately in 100% of the patients after the blood flow was restored could be a sign that the symptoms observed were related to the reduced arterial blood flow. This was confirmed during ultrasound imaging as an anechoic or hypoechoic mass of hyaluronic acid was visible in the perivascular space before the targeted treatment and was absent after the treatment. In addition, when using Doppler ultrasound imaging, a restoration of normal blood flow was observed which coincides with the improvement of clinical symptoms. Therefore, a connection between arterial blood flow and clinical symptoms can be confirmed, which is in line with currently accepted pathophysiologic mechanisms.[5,6,18,19] However, the model by which the arterial blood flow is affected by the aesthetic treatment could be revisited based on the observations made herein.

The hyaluronic acid material was identified in the perivascular space and not inside the artery; however, the clinical symptoms were visible at the skin surface and in the soft tissues supplied by that respective artery. In line with previous surgical experience in flap surgery, this model might be comparable to the perforasome concept[20] which was initially derived from the angiosome theory by Taylor et al and many other excellent researchers.[21–24] The perforasome concept suggests that one artery (the perforator) provides blood supply to a distinct area of soft tissue (the perforasome) which depends on the blood supply of that specific vessel for survival.[20,25,26] The ultrasound investigations performed for the purposes of this study (adverse vascular event management) revealed that targeting the main arterial trunk allows for immediate clinical improvement of the symptoms once the arterial blood flow is restored; this was not the case when the soft tissues were treated via the "flooding" protocol. The "ultrasound-guided targeted" protocol, however, aims to apply hyaluronidase under ultrasound guidance for that specific blockage. Once this blockage was resolved, immediate improvement in blood flow (<60 seconds) and clinical symptoms occurred.

It can be argued that the clinical improvement resulted from diffusion of hyaluronidase into the arterial blood stream as suggested in 2014 by DeLorenzi,[27] who refuted the applicability of the perforasome concept for adverse vascular events following soft tissue filler injections.

However, the following arguments can be presented to support the perforasome concept: (1) in the present study we utilized ultrasound imaging to visually identify and resolve the filler material; (2) the half-life of hyaluronidase in plasma is 2-3 minutes,[12,13,27–29] which would be insufficient to dissolve up to 1.0 mL of hyaluronic acid material; (3) administering hyaluronidase superficially with the "flooding" protocol did not resolve the clinical symptoms (whereas the targeted protocol did); and (4) once the filler material was dissolved, immediate restoration of normal blood flow occurred in the soft tissues supplied by the perforator artery, ie within the perforasome.

When investigating the relationship between injection site and clinical symptom site, it was revealed that in 33 (84.6%) cases, the skin symptoms presented in the same location as the injection was performed, whereas in 6 (15.4%) cases, the skin symptoms surfaced in adjacent areas (Table 3). These manifestations were previously attributed to a direct vascular connection having a common and continuous arterial bloodstream connecting one area to the other. This mechanical concept might be worth reconsidering given the availability of the perforasome concept and based on the results presented in this study. The mechanical concept, however, is based on the assumption that the filler material is obstructing the arterial blood flow by itself due to its presence inside the artery. Its degradation (with hyaluronidase) results in its breakdown and the now smaller particles are washed downstream along with the reinstituted arterial blood flow; this can coincide clinically with the presentation of skin surface symptoms. The careful interpretation of the results presented herein reveal inconsistencies in this mechanical concept. The hyaluronidase was injected in 100% of the cases in the perivascular space and not inside the arterial bloodstream. After the identified filler material was dissolved, the clinical symptoms improved immediately without residuals. It could be argued that the injected hyaluronidase diffused into the artery and consequently dissolved the intra-arterially located hyaluronic acid or reduced its size into globules which allowed for restoration of the blood flow. Counter-arguments for this are that the filler material needs time to dissolve depending on its rheologic properties and on the injected volume; both factors were shown not to be of relevance when performing the "ultrasound-guided targeted" protocol. This could rather indicate that the more likely concept is the "vasospasm" concept in a perforasome anatomic arrangement: the filler material seems to have the ability to cause, either by itself or in combination with a mechanical vessel injury, or due to other unknown reasons, a vasospasm of the artery. The vasospasm of a perforator can reduce or block the arterial blood supply to the consecutive perforasome with the resulting clinical effects observed either in the adjacent or in the further proximity of the initial filler injection. Removal of the filler material resulted in the termination of the vasospasm, which allowed for immediate restoration of the blood flow and immediate improvement of the clinical symptoms.

It is hoped that this study will lead to new investigations which will elaborate further on the perforasome concept and will hopefully result in the identification of facial perforasomes similar to the concept of the facial angiosomes.[25,26] Once facial perforasomes and their contributing arteries are identified, a faster and more targeted management of adverse vascular events can be initiated to ultimately ameliorate the clinical, emotional, and social stigma that patients potentially carry following adverse vascular events caused by soft tissue filler injections.

However, this study is not free of limitations. The difference in outcome between the 2 investigated hyaluronidase protocols could be a result of the limited effectiveness of the "flooding" protocol due to its incorrect/insufficient execution. Despite being taught and emphasized by various societies and boards, the protocol could have been incorrectly carried out, introducing a bias toward the "ultrasound-guided targeted" protocol. It should be emphasized that this study is a clinical observation and not an experimental or laboratory study. Following the instructions of a protocol can be influenced by many factors that are reflective of real-life conditions, and its proper execution can have limitations. However, these limitations represent best the events during and following adverse events in daily clinical practice with its insecurities, shock, and fear. These influencing factors are absent in a laboratory setting, and therefore it can be assumed that real-life situations have limitations, especially when it comes to accurately following a protocol. The adverse events presented in this study are not different from those of any other country, region, specialty, or medical field; they can unfortunately happen everywhere and to anyone. The authors therefore feel that this study is genuinely reflective of unbiased, real-life clinical scenarios.

Another limitation of this study is that the presence or the location of a blood thrombus was not assessed. It could be argued that the reduced arterial blood supply and its clinical consequences are worsened and/or perpetuated by the presence of blood clots. This might become clinically even more relevant when the time before an effective treatment is administered is prolonged. Given the time constraints of beginning with the "ultrasound-guided targeted" protocol, and the specific focus on the facial vascular system and on the identification of the filler material, no additional ultrasound-based investigations to detect thrombi were performed by the authors. Future studies will need to investigate this additional aspect in the management of adverse vascular events, especially because a previous study has indicated that the combination of

hyaluronidase (for hyaluronic acid–based material) and urokinase (for blood-derived thrombi) was helpful in alleviating impairment of a patient's vision following soft tissue filler–induced visual compromise.[30] It is, however, questionable whether thrombi are visible during ultrasound imaging while managing adverse vascular events given the small diameter of facial vessels and the reduced blood flow of the affected tissue when investigated with Doppler color-coded imaging. What was observed while performing the "ultrasound-guided targeted" protocol was a hypoechoic to isoechoic, partly well-defined round mass in the perivascular space that is identical to injected filler material; this mass was targeted under direct ultrasound guidance. The immediate improvement of clinical symptoms after the application of hyaluronidase alone reduces the likelihood of a thrombus being the major culprit when focusing on the results presented herein.

Another limitation of this study is that it is unclear at this point whether the "ultrasound-guided targeted" protocol is helpful for other body regions, for late-stage cases, or for cases where a visual compromise is involved. It is hoped that this protocol will be helpful, but future cases (which will unfortunately occur) will guide this path. Basic sciences (eg, anatomy) and clinical specialties (eg, dermatology, plastic surgery, radiology) will have to go hand in hand to improve treatment strategies and to come up with solution for a better patient treatment and adverse management outcome.

CONCLUSIONS

This retrospectively evaluated case series revealed that an "ultrasound-guided targeted" protocol for the treatment of adverse vascular events following hyaluronic acid–based soft tissue filler injections utilized less hyaluronidase material and restored clinically visible symptoms more rapidly. The performed Doppler ultrasound imaging assessment additionally revealed that once the filler material is dissolved, normal blood flow is restored, which coincides with the improvement of the clinical symptomology. The effect of the "ultrasound-guided targeted" protocol is best explained by the perforasome concept, which will need to be investigated further in future studies.

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