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ORIGINAL CONTRIBUTION

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Managing intravascular complications following treatment with calcium hydroxylapatite: An expert consensus

Jani van Loghem MD[1] | David Funt MD[2,3,4] | Tatjana Pavicic MD[5] | Kate Goldie MD[6] | Yana Yutskovskaya MD[7] | Sabrina Fabi MD[8] | Pieter Siebenga MD[1] | Job Thuis MD[1] | Joseph Hkeik MD[9] | Jonathan Kadouch MD[10] | Welf Prager MD[11] | Nabila Azib MD[12] | Gabriela Casabona MD[13] | Steve Dayan MD[14] | Shino Bay Aguilera MD[15] | Philippe Snozzi MD[16] | Peerooz Saeed MD[1,17]

[1]Falck Clinic, Aesthetic Medicine Centre, Amsterdam, The Netherlands

[2]Mount Sinai School of Medicine, New York, NY, USA

[3]Mount Sinai School of Medicine, Garden City, NY, USA

[4]Mount Sinai School of Medicine, Woodmere, NY, USA

[5]Private Practice for Dermatology and Aesthetics, Munich, Germany

[6]European Medical Aesthetics Ltd, London, UK

[7]Dermatovenerology and Cosmetology Department, Pacific State Medical, University of Health, Moscow, Russia

[8]Department of Dermatology, University of California, San Diego, CA, USA

[9]All Saints Clinic, Double Bay, Sydney, NSW, Australia

[10]ReSculpt Clinic, Practice for Aesthetic Dermatology, Amsterdam, The Netherlands

[11]Prager & Partner Dermatologische Praxis, Hamburg, Germany

[12]Dr. Azib Private Praxis, Rabbat, Morocco

[13]Scientific Department, Ocean Clinic, Marbella, Spain

[14]Division of Facial Plastic and Reconstructive Surgery, Department of Otolaryngology, University of Illinois at Chicago, Chicago, IL, USA

[15]Department of Dermatology, Nova Southeastern University College of Osteopathic Medicine, Fort Lauderdale, FL, USA

[16]Smoothline Clinic, Zürich, Switzerland

[17]Departments of Ophthalmology and

Abstract

Background: Inadvertent intra-arterial injection of dermal fillers including calcium hydroxylapatite (CaHA) can result in serious adverse events including soft tissue necrosis, permanent scarring, visual impairment, and blindness. When intra-arterial injection occurs, immediate action is required for optimal outcomes, but the infrequency of this event means that many physicians may never have experienced this scenario. The aim of this document is to provide evidence-based and expert opinion recommendations for the recognition and management of vascular compromise following inadvertent injection of CaHA.

Methods: An international group of experts with experience in injection of CaHA and management of vascular complications was convened to develop a consensus on the optimal management of vascular compromise following intra-arterial CaHA injection. The consensus members were asked to provide preventative advice for the avoidance of intravascular injection and to produce a treatment protocol for acute and delayed presentation. To ensure all relevant treatment options were included, the recommendations were supplemented with a PubMed search of the literature.

Results: For prevention of intra-arterial CaHA injection, consensus members outlined the importance of a thorough knowledge of facial vascular anatomy and patient history, as well as highlighting potential risk zones and optimal injection techniques. Individual sections document how to recognize the symptoms of vascular occlusion leading to vision loss and tissue necrosis as well as detailed treatment protocols for the management of these events. For impending tissue necrosis, recommendations are provided for early and delayed presentations with treatment protocols for acute and follow-up treatment. A separate section details the treatment options for open and closed wounds.

Endocrinology, Orbital Center, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Correspondence
Jani van Loghem, Falck Clinic, Aesthetic Medicine Centre, Falckstraat 51, Amsterdam, The Netherlands.
Email: jani@falckclinic.com

Conclusions: All physicians should be prepared for the eventuality of intra-arterial injection of a dermal filler, despite its rarity. These consensus recommendations combine advice from aesthetic experts with the latest reports from the published literature to provide an up-to-date office-based protocol for the prevention and treatment of complications arising from intra-arterial CaHA injection.

KEYWORDS
calcium hydroxylapatite, dermal filler, intra-arterial injection, safety, vascular compromise, vision loss

1 | INTRODUCTION

In the past two decades, the popularity of injectable dermal fillers to correct aging-related soft tissue volume loss and contour defects has increased dramatically. Along with neurotoxin injections, these products represent the mainstay of most medical aesthetic practices.[1,2] Among the soft tissue fillers, hyaluronic acid (HA) products are most commonly used, followed by calcium hydroxylapatite (CaHA, Radiesse®; Merz North America, Inc) and poly-L-lactic acid (Sculptra, Galderma®).[1,2] Although these products are considered to be safe (within their approved indications and when injected by qualified professionals), the potential risk for severe adverse events remains regardless of the filler used.[3,4]

In a cross-sectional review, the complication profile associated with injectable fillers was evaluated by searching the databases of the US Food and Drug Administration (FDA) and Manufacturer and User facility Device Experience (MAUDE). From 2014 to 2016, a total of 1748 adverse events were reported.[5] Intra-arterial injections without sequelae and those resulting in necrosis or blindness were considered severe complications and were reported in 220, 121, and 8 cases, respectively, the latter most commonly after dorsal nasal injections.

Vascular compromise and occlusion may occur with any dermal filler following inadvertent intra-arterial injection, and it is generally the volume of product injected rather than filler type that has the greatest impact: The larger the bolus and the larger the branch of the artery that is embolized, the larger the area of necrosis. All injectors must be aware of the type of adverse events that can occur and how to treat them. A comprehensive understanding of facial anatomy and dermal filler characteristics is essential. Given the rarity of vascular compromise, physicians might not have any experience in the recognition nor management of these complications.

For hyaluronic acid based fillers, a number of aesthetic physicians have proposed protocols for the management of vascular compromise using hyaluronidase,[6-9] and several consensus documents have been published.[10-13] Treatment protocols have been proposed for vascular compromise following CaHA injections,[6,14,15] but to date no specific consensus guidelines exist.

2 | CONSENSUS OBJECTIVES AND METHODOLOGY

CaHA is one of the most versatile dermal fillers with a long history of aesthetic use.[16,17] It is widely used for indications ranging from volumizing and contouring, and more recently in hyperdiluted form for skin rejuvenation.[18-21] The risk of severe adverse events as a result of inadvertent intra-arterial injection is very rare, but all injectors using this product should have an in-depth understanding of how this may occur, how to avoid it, how to recognize it, how to limit vascular compromise should it occur, and how to treat the resulting sequelae. The current recommendations have addressed this need by bringing together a group of 17 international aesthetic experts with experience in injection of CaHA and the management of CaHA-related complications. The format was slightly different from most consensus papers in that there were no face-to-face meetings. The process was initiated in November 2018 when consensus members were asked to produce a treatment protocol for immediate and late measures to be taken after intra-arterial injection of CaHA, and to give preventative advice for the avoidance of intravascular injection. A comprehensive literature search was also conducted using the PubMed database and the following search terms: calcium hydroxylapatite, Radiesse, vascular compromise, vascular occlusion, vascular necrosis, visual impairment, vision loss, and blindness; articles were limited to those published in English. A first draft was prepared based on the information collected and a draft circulated to the group for their comments and precision. Areas of disagreement were identified and a questionnaire circulated allowing members to vote on contentious areas.

The current document represents the culmination of this process. In light of new scientific knowledge, treatments for filler-induced vascular compromise are constantly improving. The aim of this paper was to collate all successful treatment options into one document and based on this information to provide an up-to-date protocol for treatment based on expert consensus and the latest treatment techniques. Ethics approval was not required for this consensus statement. The specific recommendations presented in this article represent the panel's expert opinion based on their collective clinical experience and published data regarding vascular compromise with CaHA in the cosmetic setting. All patients whose

images appear in this document provided written informed consent to their use.

2.1 | Calcium hydroxylapatite aesthetic indications

Approved aesthetic indications of CaHA are for facial soft tissue augmentation including the correction of moderate-to-severe facial wrinkles and folds, such as nasolabial folds and to correct volume loss in the dorsum of the hands.[22-24] With the recognition that facial aging occurs at all anatomical layers, expanded, albeit off-label indications, for CaHA, have been developed that make use of its rheological properties, and in addition to soft tissue lifting, it is now also widely used to restore contours affected by age-associated bone resorption, replenish fat loss, and most recently in diluted form to improve skin laxity. The product's instructions for use warn that special care should be taken to avoid injection into the vasculature, particularly in high-risk areas that are dependent on blood supply from a single arterial branch such as the glabellar, nose, and nasolabial folds.[25] However, all facial arteries are potentially vulnerable to intravascular injection and once the pressure from injection has ceased, the product travels through the vasculature and may result in local or distal necrosis. Intravascular occlusion of facial arteries is solely due to injector-dependent technical errors and can be avoided with a comprehensive knowledge of vascular anatomy and proper injection technique.

3 | RESULTS

3.1 | Prevention

3.1.1 | Anatomy and patient history

A thorough discussion of the facial (three-dimensional arterial) anatomy relevant to dermal filler injections is beyond the scope of this review, but the reader is referred to a series of publications based on anatomical dissections designed to promote safe patient outcomes after nonsurgical aesthetic treatment, a number of which were co-authored by members of this consensus group and are relevant to facial areas typically treated with CaHA injections.[26-34]

A complete patient medical history should be obtained at the initial consultation including details of all previous aesthetic treatments and surgery as these can alter the patient's baseline anatomy. Physicians should also be aware that there are large variations between individuals in the branching patterns of many arteries.[35,36] Patients who have undergone previous cosmetic procedures such as rhinoplasty may have unpredictable repositioning of blood vessels and a more tenuous blood supply in the operated area, which may increase the risk of ischemia, necrosis, and vascular embolism following the filler injection.[37] Previous tissue scars may also fix arteries in place, making them easier to penetrate with small sharp needles or even cannulae.

3.1.2 | Risk zones

Areas of the face that have the highest risk of vascular occlusion are those with extensive anastomoses between vascular territories (Figure 1), because of the risk of occluding adjoining smaller diameter arteries, for example, central retinal artery,[8] and those with a poor source of collateral circulation,[5,38,39] such as the end arteries of the nasal tip and alar (Table 1). Injections to the nasal area have been reported as the main cause of tissue necrosis and the second cause of visual loss.[40,41]

The glabella is a contraindication for CaHA, and the product should not be injected here. The glabella is the most common filler injection site triggering blindness as small vessels branching from the supratrochlear artery provide the blood supply to the glabellar region and connect to the central retinal artery via the ophthalmic artery. In the area of the nasolabial fold and nasal dorsum, there are anastomoses between the facial, angular, and lateral nasal arteries (external carotid circulation) with the dorsal nasal artery, which is a branch of the ophthalmic artery (internal carotid circulation) (Figure 2).[32] Injection into the nasolabial fold or nasal dorsum may therefore accidentally deliver product intra-arterially, and if plunger pressure is greater than arterial pressure, product can move proximally into the central retinal artery. In the temporal region, anastomoses can exist between the frontal branch of the superficial temporal artery and the supraorbital, supratrochlear, and zygomaticotemporal arteries (Figure 2), thus allowing a filler to be propelled retrograde into the central retinal artery.[32]

To minimize risk, injections should always be performed slowly, with low volume and attention paid to the pain feedback received from the patient. Close to the supratrochlear and supraorbital foramina, no injection should be performed in the supraperiosteal and subgaleal planes, respectively.[42,43]

3.1.3 | Injection technique

For a detailed description of the anatomical planes that offer the least arterial risk in injection danger zones, the reader is referred to the papers of Criollo-Lamilla et al and Cotofana & Lachman.[33,44] Needles are no longer recommended for injecting the forehead. Studies have shown that injected product changes plane after needle injections and does not remain in the subgaleal (safe) plane.[45] This has been demonstrated with a range of needle sizes and with injections performed at both perpendicular and oblique angles.[46] A recent cadaver study, which compared the forces required to penetrate the facial arterial vasculature, found that all sizes of cannula with the exception of 27G required greater forces for intra-arterial penetration compared with correspondingly sized needles; 27G cannulas required a similar force to a 27G needle.[34] Van Loghem et al[47] suggest the use of a cannula when treating the frontal area and have published techniques for injections in this zone.[43]

CaHA should be injected slowly, with a low injection force and with the smallest amount of product necessary. For deep injections, the

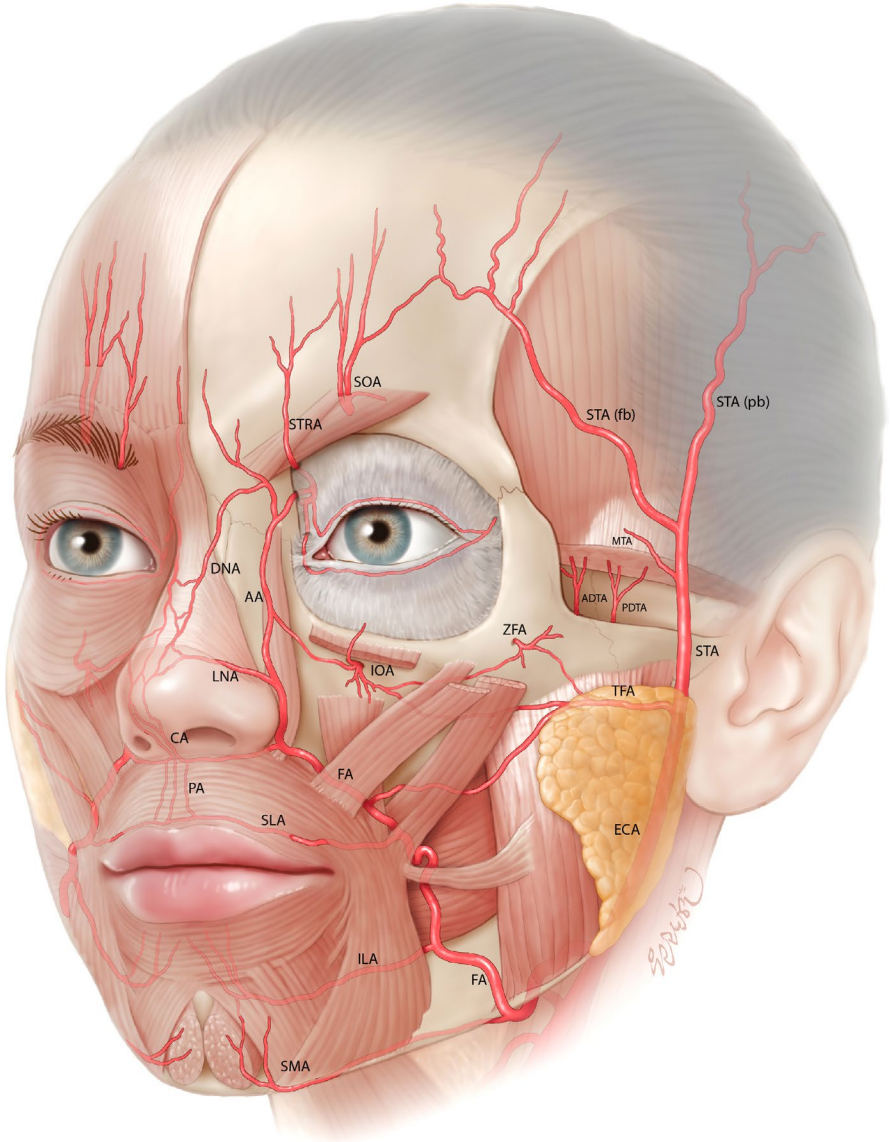


FIGURE 1 Illustration of the main facial arteries and their anastomoses. (fb), frontal branch; (pb), parietal branch; AA, angular artery; ADTA, anterior deep temporal artery; CA, columellar artery; DNA, dorsal nasal artery; ECA, external carotid artery.; FA, facial artery; ILA, inferior labial artery; IOA, infraorbital artery; LNA, lateral nasal artery; MTA, middle temporal artery; PA, philtral artery; PDTA, posterior deep temporal artery; SLA, superior labial artery; SMA, submental artery; SOA, supraorbital artery; STA, superficial temporal artery; STRA, supratrochlear artery; TFA, transverse facial artery; ZFA, zygomaticofacial artery. Copyright Jani van Loghem, UMA-Institute.com

periosteum remains the preferred location, but with caution as there is no guarantee that injections will be extravascular or remain on the periosteum.[46] Large boluses should be avoided and injection volumes limited to 0.1 mL. Although flow of product can be reduced by using the smallest gauge needle size possible, small needle caliber increases plunger pressure and the likelihood of clogging, which may cause the injector to increase the pressure on the plunger and thus the risk of serious adverse events should the needle be intravascular. Large gauge needles increase the risk of bruising, but might decrease the risk of intravascular injections. If unexpected resistance is detected, blanching observed, or the patient indicates pain, the injection must be stopped immediately.

Aspiration is often advocated as a method of avoiding intravascular injection, the appearance of blood in the syringe indicating the needle has entered an artery. However, it is important to note that the absence of blood in the needle hub on aspiration is no guarantee of avoidance. This has been demonstrated by the results of a recent in vitro study where nondiluted CaHA (with and without integrated lidocaine) showed negative test results with anticoagulated blood with a variety of needles (23-33G), even after 10 seconds of aspiration with 0.5 mL negative pressure.[48] CaHA with standard dilution (16.7% lidocaine) showed positive test results within 1 second using needles of 27G or thicker with a 0.8 mL CaHA syringe and aspiration times of 3 seconds (27G, 13 mm and 25G, 13 mm) and 7 seconds (23G, 19 mm) with the 1.5-mL syringe. Some research has suggested that a slow-pull retraction and up to 5 seconds waiting time may improve the reliability of the aspiration test.[49]

Aspiration test results are influenced by needle diameter, needle length, syringe, and rheological properties of the filler material, making general remarks on reliability of aspiration difficult, other than to conclude that aspiration is unreliable.[48,50] A blunt-tip cannula (22-25G) and not a sharp needle should be used for injections in risk zones, for example, when in proximity to the foramina.

The use of blunt cannulae decreases the risk of intravascular injection, but all cannulae (except the 10G size) can enter arteries

TABLE 1 Risk zones for injection

Area	Indication	High risk	Average risk	Low risk	Lowest risk anatomical level
Frontal area	Frontal concavity [2]	SOA (sf), STRA (sf)	SOA (d), STA (d)[a]		Supraperiosteal
Periorbital area	Brows [2]		SOA (d) STA (frontal branch sf)		Supraperiosteal,
	Glabella [3]	STA (d)			Contraindicated
	Tear troughs [2]		IOA (d), AA (sf)		Supraperiosteal[b]
	Palpebromalar groove [2]		ZFA (d)		Supraperiosteal
Temporal area	Temporal hollows [1]		STA (sf), ADTA (d), PDTA (d)	STA (if)	Interfascial[c]
Nose	Nasal tip [2]	LNA (sf), CA (sf)			Not recommended
	Nasal dorsum [2]	DNA (sf)			Supraperiosteal
	Alar [2]		LNA (sf)		Not recommended
	Columella [2]		CA (sf)		Sub-SMAS
Cheeks	Lateral cheek			ZFA (d), TFA (d)	Supraperiosteal, subcutaneous
	Medial cheek		IOA (d) FA (sf) AA (sf)		Sub-SMAS, subcutaneous (diluted)
	Nasolabial folds		SLA (d) FA (sf) AA (sf)		Supraperiosteal
Mandibular area	Mandibular angle		ECA (d) FA (d)		Subcutaneous
	Pogonium		ILA (d)		Supraperiosteal, subcutaneous
	Mentum		SMA(d), ILA (d)		Supraperiosteal, subcutaneous
	Marionette lines		SMA(d), ILA (d), FA (d)		Subcutaneous
	Prejowl sulcus		SMA(d), ILA (d), FA (d)		Supraperiosteal, subcutaneous

Note: Commonness of indication: [1] regular CaHA indication; [2]: not a common CaHA indication; and [3]: contraindication for CaHA.

Usual depth of the artery: (sf): superficial: subcutaneous, (d): Deep: underneath the superficial musculo-aponeurotic system (SMAS), (if): interfascial. Arteries and their branches.

Abbreviations: AA, angular artery; ADTA, anterior deep temporal artery; CA, columellar artery; DNA, dorsal nasal artery; ECA, external carotid artery; ILA, inferior labial artery; IOA, infraorbital artery; LNA, lateral nasal artery; PDTA, posterior deep temporal artery; SLA, superior labial artery; SMA, submental artery; SOA, supraorbital artery; STA, superficial temporal artery; STRA, supratrochlear artery; TFA, transverse facial artery; ZFA, zygomaticofacial artery.

[a]Deep, subgaleal should be the safest plane of injection, but considering other risk factors like multi-level trajectory of the STRA and SOA in the 2 cm superior to the supraorbital rim not regarded as lower risk.

[b]Even though this is theoretically correct, there are only 3 anatomical layers. The risk of CaHA ending up in the subcutaneous plane and being visible or causing malar edema is therefore significant.

[c]Anatomically, the interfascial plane is avascular and therefore the safest. However, as the STA is attached to the temporoparietal fascia, this level is crossed by the cannula when traveling from the skin to the target plane and may therefore be less safe than the subcutaneous plane.

and are therefore not 100% safe.[34,51] Cannulae 25G or larger require greater force to enter a vessel than a needle, while smaller cannulae 27G and 30G are similar to needles. Parallel injections to the direction of the local arteries should be avoided as well as using force through resistances that could contain arteries. Areas where arteries have limited space to be pushed aside pose a particular risk, including postsurgical areas and neurovascular bundles.

Other options to decrease the risk of vascular compromise include injecting in a retrograde fashion with a constantly moving needle so as not to deliver a large deposit in one location. The use of adrenaline (epinephrine)-containing local anesthesia promotes arterial constriction, reducing the size of vessels and therefore the risk of filler entry. However, products containing adrenaline may mask blanching produced by occlusion.[52] Tumescent injection, also known as saline hydrodissection, has been used successfully when performing CaHA injections of the forehead.[53,54] The tumescent solution for tissue hydrodissection creates a pocket of space for filler placement and allows the physician to reduce bleeding and prevent vessel compromise.

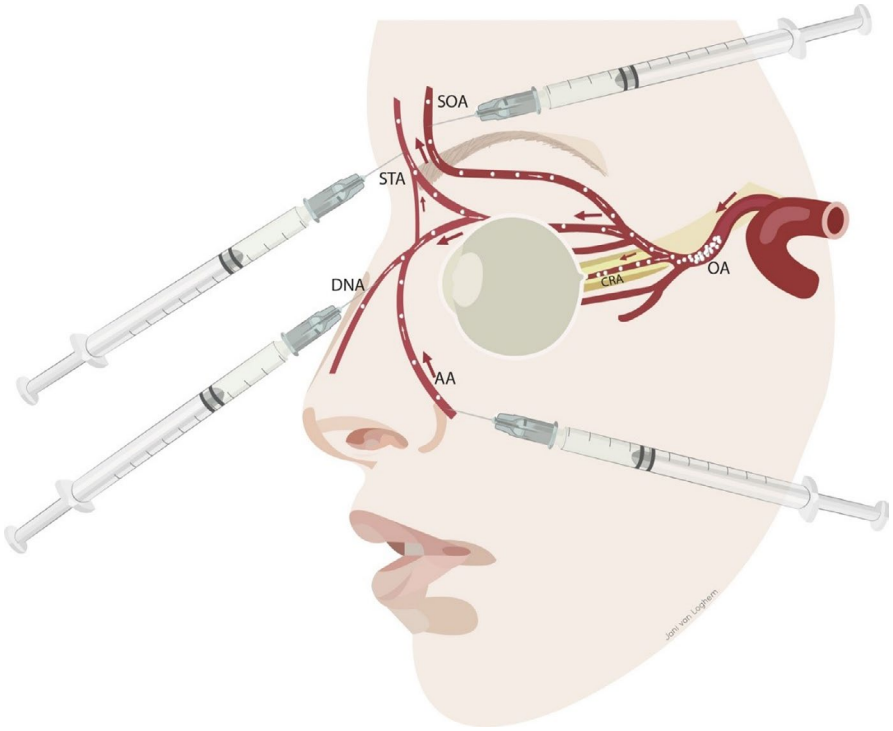


FIGURE 2 Possible pathways of central retinal artery embolization. AA, angular artery; CRA, central retinal artery; DNA, dorsal nasal artery; OS, ophthalmic artery; SOA, supraorbital artery; STA, supratrochlear artery. Red arrows: direction of blood flow; white arrows: direction of filler displacement. Copyright Jani van Loghem, UMA-Institute.com

3.2 | Vascular occlusion leading to vision loss

3.2.1 | Recognizing the symptoms

A disruption of the blood supply to the retina can occur after dermal filler injection in almost any area of the face and results in a sudden onset of impairment/loss of vision accompanied by severe pain (ocular, facial, and/or headache). Cerebral infarction can accompany retinal artery occlusion, and therefore, signs and symptoms such as aphasia or even contralateral hemiparesis might also be present.[55]

3.2.2 | Management of impending vision loss

Once the retinal artery has been occluded, only a short window of opportunity of about 60 minutes exists before blindness is irreversible (Figure 3).[56] Only one case report has described a partial vision recovery after CaHA-induced retinal artery occlusion, which involved application of topical and systemic intraocular pressure lowering agents, isovolemic hemodilution, ocular massage, and aspirin anticoagulation, as well as carbon dioxide inhalation, oral corticosteroids, and hyperbaric oxygen therapy.[57] The patient must be transferred immediately to the nearest ophthalmologist with as much information as possible regarding the product, injection site(s), and the volume of injection.

The goal is rapid reduction of intraocular pressure to allow the emboli to dislodge downstream and improve retinal perfusion. Acute management involves eyeball massage to promote a lowering of the intraocular pressure. The technique involves small rapid changes of intraocular pressure over a period of 1-3 hours, until all retinal emboli have been cleared from the vessel. Ocular massage is performed with the patient in a supine position, looking downward with their eyes closed.[32] Gentle pressure is applied to the sclera of the anesthetized eye with a finger, indenting the globe by a few millimeters and then releasing at a frequency of 2-3 times a second.[32,58] The prolonged, rapid small changes in intraocular pressure have been found to be more conducive to dislodging emboli than a brief high-pressure aggressive massage of the eye. The procedure should be continued until the patient reaches the treating ophthalmologist in the hospital.

An additional acute measure is to encourage the patient to "rebreathe" in a paper bag to increase carbon dioxide levels in the blood, which will cause the retinal arteries to vasodilate and could help dislodge the blockage.[32,59] The patient should be given aspirin 500 mg (Europe) or 625 mg (US) to avoid blood clotting upstream to the CaHA embolus.

Administration of a beta-adrenergic antagonist in the form of eye drops (eg, timolol 0.5%), brinzolamide, or azetazolamide will also help to reduce intraocular pressure; azetazolamide may be of greater benefit if administered intravenously, and intravenous dexamethasone may be administered to decrease inflammation. These medications may be administered in the hospital as they are not readily available in private clinics.

Oral pentoxifylline at a dose of three 600 mg tablets daily has been shown to improve retinal flow more than placebo in patients with sudden loss of vision as a result of retinal vein thrombosis, although no improvement in vision was demonstrated.[60]

(A)

CaHA Vascular Complications (Overview)

	Retinal Ischemia	Peripheral Ischemia with threatening necrosis
Diagnosis		
Symptoms	• Simultaneous occurrence of loss of vision and eye pain. • Mostly simultaneously ophthalmoparesis, ptosis, vertigo, fainting. • Peripheral ischemic symptoms may be present (blanching).	**1. Blanching phase** • Immediate, onset <1min, may be painful. **2. Livedo reticularis phase (marbling)** • After a few minutes (seldom within a few hours), due to lack of oxygen resulting in venous dilation, virtually pathognomonic. **3. Blue-grey phase** • After a few quarters of hours to two days, alternating signs of sustained lack of oxygen. **4. Pimple phase** • After 1-4 days, signs of skin necrosis. **5. Demarcation and ulceration phase** • After days to weeks, secondary wound healing.
Differential diagnosis	• Panic attack, optic neuritis, migraine, stroke or transient ischemic attack.	• Vasoconstriction due to adrenalin in anaesthesia (blanching phase). • Hematoma (blue-grey phase). • Herpes simplex lesions (pustula phase).
Therapy	• Double check vision loss. • Immediate consultation and transport to ophthalmologist. • Ocular massage: 2-3x/sec indenting the sclera a few mm until hospital. • Aspirin orally, Timolol 0.5% brinzolamide 1% eyedrops. • Rebreathe in paper bag to increase CO2 (will dilate retinal vessels). • Hospitalization and possibly i.v. therapy of PGE1, dexamethasone, oral pentoxyfilline and hyperbaric oxygen therapy.	• Hyaluronidase within a few minutes to hours. • Warm compresses. • Aspirin, tadalafil, prednisolone, pentoxyfilline. • Hyperbaric oxygen therapy, PRP, LED, RF, Laser.
How to prevent	• Use atraumatic cannulas (25G or thicker) in high-risk areas. • Gentle tissue handling. • Slow injection rate. • Small volumes: max. 0.1 ml / bolus. Periorbital close to the branches of the ophthalmic artery: max. 0.025 ml / bolus. • Sharp needle: periosteal injections: bevel down, angled approach, pull tissue away from bone, avoid foramina. • Superficial injections: intradermal. Subdermal: retrograde small amounts < 0.1 ml (avoid bolus technique). • Avoid tissue where arteries may have little room to be pushed aside like scars, neurovascular bundles, foraminae. • Periorbital area/nose: press on supratrochlear /dorsal nasal arteries with non-dominant fingers to temporarily block blood flow. • Avoid small-gauge needles and cannulas.	

(B)

CaHA Vascular Complications (Algorithm)

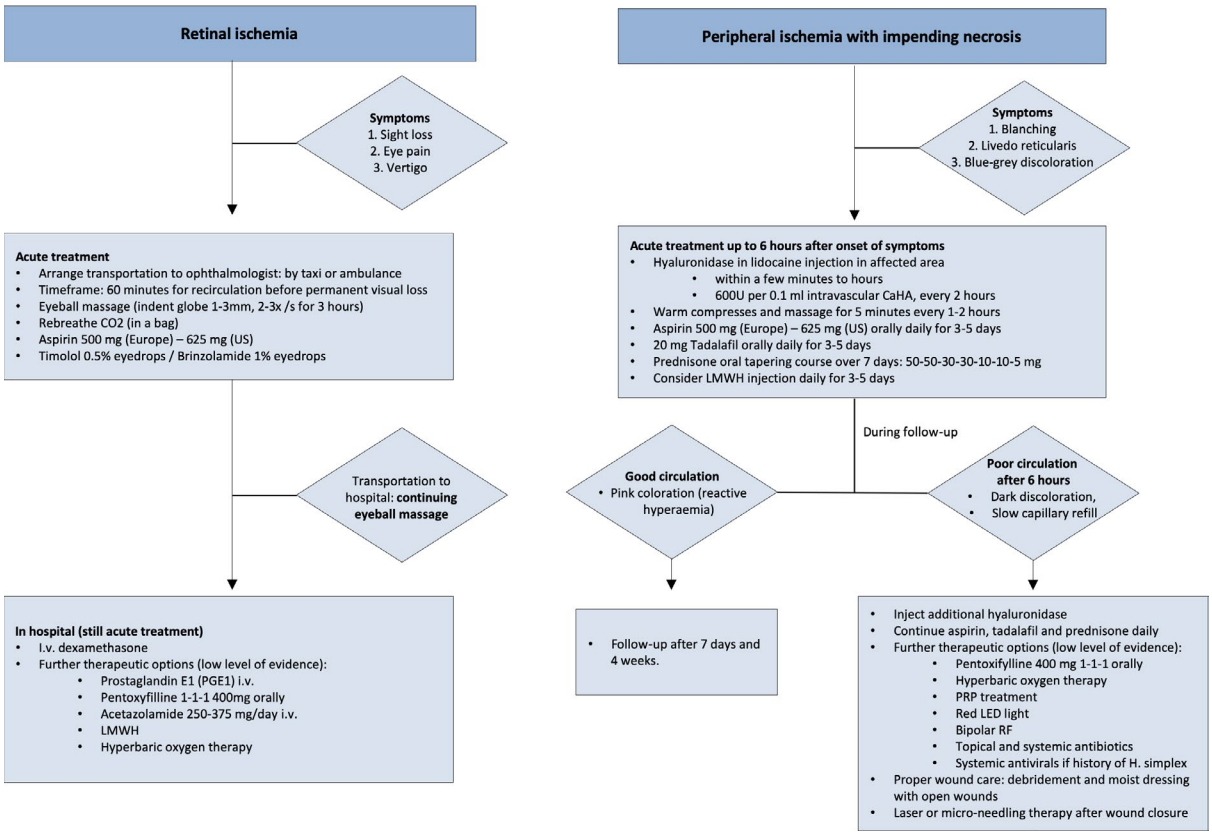


FIGURE 3 Treatment algorithm for peripheral ischemia with impending vascular necrosis and retinal ischemia with impending vision loss

3.3 | Vascular occlusion leading to tissue necrosis

3.3.1 | Recognizing the symptoms

The incidence of impending necrosis following dermal filler treatment has been estimated as 1 in 100 000 cases (0.001%),[52] although consensus members felt this estimate was too optimistic and in their experience was at least 1:10 000, particularly among less experienced injectors and when long, sharp needles are routinely used. The usual initial presentation of vascular compromise and occlusion is a disproportionate pain to what can be expected. However, the excessive pain may be masked due to the anesthetics mixed in certain fillers to an extent that in most cases, no significant pain is perceived at all. Pallor and blanching usually present themselves immediately and follow the same pattern as the restricted blood supply pathway. A livedo reaction (mottled discoloration) may follow in 1-10 minutes. Progressive symptoms include hemorrhagic changes (24-48 hours), blisters and pustules (4-6 days), and necrosis (5-10 days) (Figure 4). Finally, secondary infection may occur.

In some cases, patients may not complain of symptoms or show signs of ischemia during the filler injection or even on the day of the procedure.[15,61] A possible explanation for this delayed onset is that the filler is trapped at a bifurcation or branch point and becomes dislodged at a later timepoint to cause an occlusion.[62]

Injectors should also be aware of the potential for venous obstruction as a result of compression when excessive amounts of filler are placed in a small area. Venous obstruction is generally associated with a dull, aching pain and swelling, and a dark discoloration of the affected area and can easily be misinterpreted and dismissed as early discomfort and bruising after treatment.[63]

3.3.2 | Management of vascular compromise and impending tissue necrosis

Early presentation—acute treatment (up to 6 hours after onset of symptoms, Figure 3)

The goal is to rapidly re-instate blood flow and increase vasodilation in the affected area so treatment should commence without delay. Many of the steps will follow those recommended for impending necrosis after injection of a hyaluronic acid based product.[10-13]

In the presence of immediate pain and/or skin discoloration, or as soon as the injector suspects the blood supply has been compromised, the injection must be stopped immediately and, if possible, aspiration of the product should be attempted before withdrawing the needle. Measures should then be implemented to improve blood flow and dissipate the agent. Warm compresses should be applied and the area massaged to promote vasodilation and perfusion. Massage causes vasodilation and may be effective if a larger branch of an artery is blocked, and filler material can be spread to a few arterioles.

The area where the circulation of blood supply appears to be reduced should be flooded with hyaluronidase regardless of the filler type, due to its edema-reducing[64,65] and anti-inflammatory properties.[66] The amount of hyaluronidase will depend on the volume of CaHA injected. The hyaluronidase may be injected directly into the affected site. There was strong consensus for high doses (600U of hyaluronidase for every 0.1 mL CaHA) in the affected area, with aggressive treatment in the early stages following a vascular event. It is also important to check the reperfusion every 30-60 minutes posthyaluronidase treatment. If no improvement (eg, less blanching, improvement of capillary refill) is seen within 60 minutes, additional quantities of a hyaluronidase should be injected every 2 hours (repeat 3-4 cycles).

Aspirin should be used to limit platelet aggregation, clot propagation, and further compromise, but should be given with an antacid regimen for stomach protection. The recommended immediate treatment is with 650 mg (USA) or 500 mg (Europe, Canada) enteric-coated aspirin.[8] This should be followed by a maintenance dose of 75 mg (USA) and 100 mg (Europe) for 3-5 days. Drugs such as sildenafil and tadalafil can be used to induce smooth muscle relaxation, dilate blood vessels, and increase blood flow.[14] Subcutaneous injection of a low molecular weight heparin such as nadroparin (Fraxiparine) can be used to prevent thrombus formation proximal to the embolus and should be injected within 4 hours of the intravascular event.[38]

Consensus was not achieved on the application of topical nitroglycerin paste to facilitate vasodilation. Topical nitroglycerin may reduce tissue necrosis as a result of its vasodilatory properties with the amount dependent on the size and area of impending necrosis. However, animal studies have noted no improvement in perfusion after topical application of nitroglycerin paste.[67] In addition, application is not without side effects, such as headaches, hypotension, and dizziness. Coadministration of phosphodiesterase inhibitors with nitroglycerin is contraindicated as it can result in severe hypotension. At this time, no clear recommendations can therefore be made.

There was strong consensus for a tapering course of oral corticosteroids such as prednisone if tissue edema is present with a suggested starting dose of 50 mg, tapering the dose every other day for a maximum of 7 days. Consensus members mention that even though edema is reduced using corticosteroids, there is no evidence that they have a positive effect on the outcome of ischemia after CaHA injection. There was also consensus on prescribing prophylactic antiviral medication such as valaciclovir in patients with a history of herpes simplex virus and if the affected tissue involves the oral or nasal mucosa.

Early presentation—treatment follow-up

If after 6 hours circulation remains poor, hyaluronidase, aspirin, tadalafil, and the prednisolone tapering course should be continued. There are also a number of additional therapeutic measures that can be considered that may improve outcome of CaHA-induced impending necrosis.

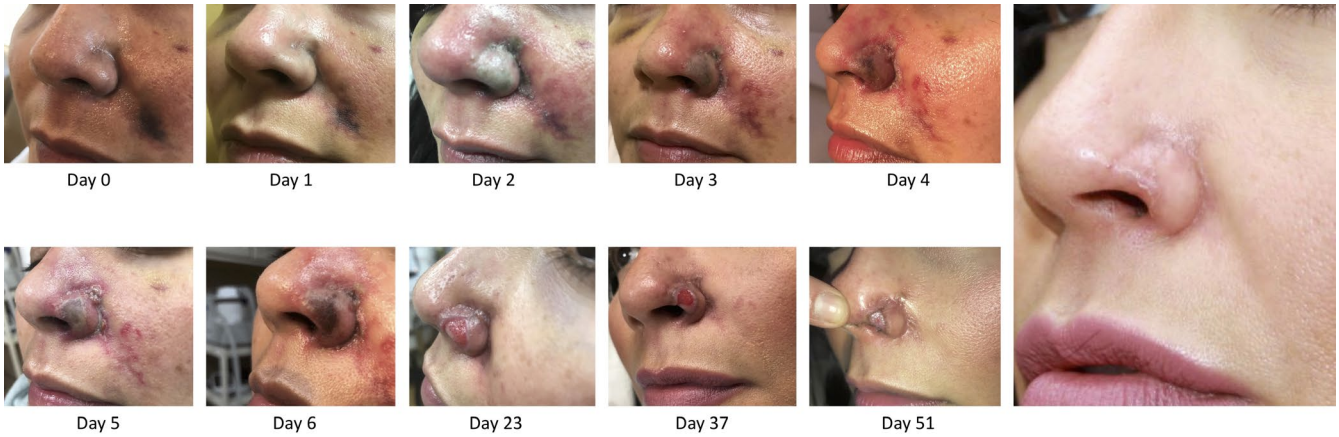


FIGURE 4 Sequence of events in the development of vascular necrosis (courtesy of David Funt). The patient suffered a facial artery embolization with ischemia of the ala following injection in the nasolabial fold, near the pyriform aperture, with CaHA using a sharp needle. Initially, she was treated with massage, warm compresses, oral sildenafil 50 mg daily for 4 d, nitroglycerin paste for 4 d, oral antibiotics, valaciclovir prophylaxis, and open treatment with aquaphor and twice-daily showering. This demonstrates that early debridement should be avoided because patients usually heal better than initially anticipated

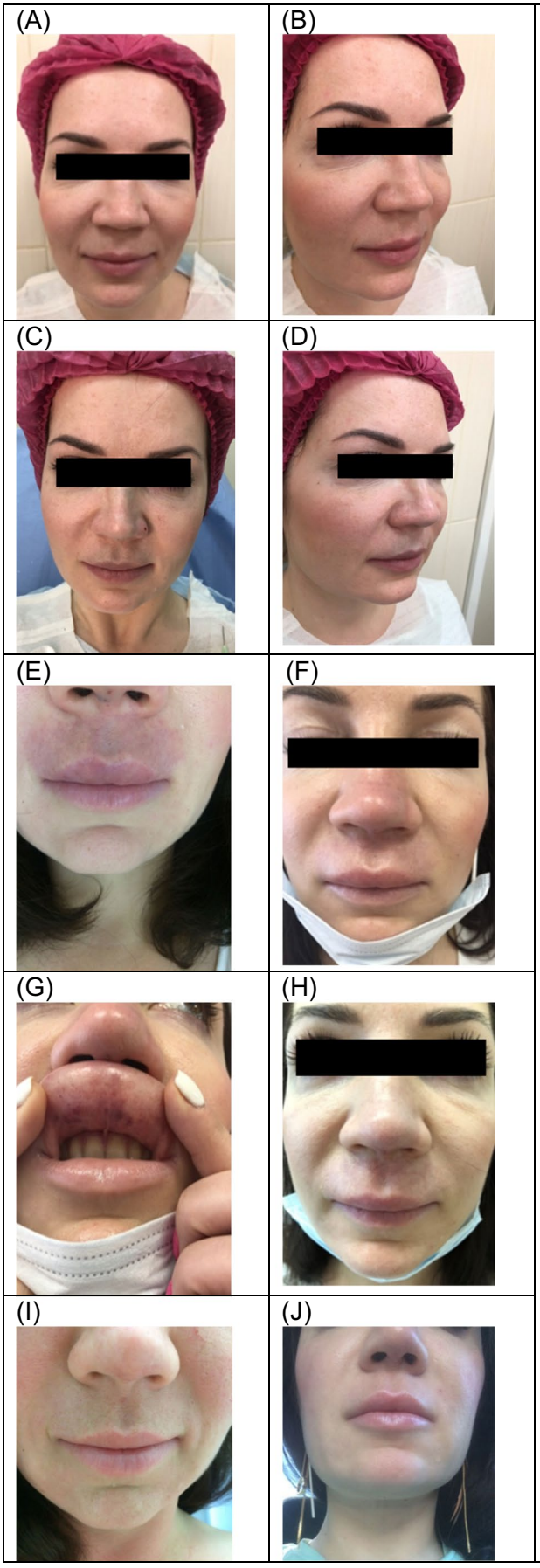
- Without signs of severe necrosis, there was no consensus on the use of systemic antibiotics. If the clinical picture of the ischemia suggests a favorable course, superinfection is very unlikely.
- There was no consensus on the use of antibiotics with anti-inflammatory properties like doxycycline to treat CaHA-induced ischemia as there is no published evidence to support this.
- There was consensus about the use of systemic antibiotics in the event of signs of severe necrosis. Some authors advised antibiotics with a strong microbiological action like ciprofloxacin or clarithromycin.
- Pentoxyfilline (Trental®) 400 mg three times daily may accelerate healing of soft tissue necrosis by improving erythrocyte flexibility and increasing tissue oxygen levels.[68]
- Hyperbaric oxygen therapy (oxygen therapy under pressure) should be considered.[66,69] This has the potential to deliver oxygen deep into the skin to oxygenate ischemic tissue, reduce edema, and promote angiogenesis. It should be initiated in those cases where the involved tissue appears dusky the day after the event despite the institution of the above measures.
- Another procedure that has been used successfully to promote healing of necrotic tissue is the use of platelet-rich plasma (PRP). PRP therapy involves drawing blood from the patient, running it through a centrifuge to obtain a plasma fraction with a concentrated platelet count and high levels of cytokines and growth factors, which are re-injected at the site of tissue injury. PRP has been shown to improve healing of wounds, tendons and bone.[70] In one case report, PRP was injected intradermally and applied topically to the skin of a 46-year-old woman who had developed necrosis on the glabella, forehead, and dorsum of the nose after injection of hyaluronic acid filler 2 days previously.[71] The patient was initially treated with hyaluronidase, oral antibiotics, and prednisolone, which could not prevent deterioration of the wound. After debridement, the patient received PRP on the fourth day after the onset of the adverse event. Although the patient required several treatments with a carbon dioxide laser, the combination of PRP with standard treatments for tissue necrosis appeared to accelerate scar resolution.
- Red light therapy, for example, with a 640-nm light emitting diode (LED) red light source, can be used to decrease inflammation. This has been shown to improve vascular circulation and promote wound healing for necrosis following breast reconstruction surgery,[72] and may be beneficial for impending filler-induced tissue necrosis.[66]
- One of the consensus authors (SF) indicated that monopolar radiofrequency with a rolling method may be beneficial in dilating blood vessels, but as there is no published evidence on this, radiofrequency is not included in the algorithm.

All patients should be monitored closely for progress and for signs of infection. They must strictly avoid exposure to nicotine either from smoking tobacco, vaping, patches, or second hand smoke. They should also avoid exposure to extreme cold as compromised tissues are more prone to frostbite injury.

Two of the consensus authors (YY and DF) have included case reports in this article describing the development of necrosis following injection of CaHA for nasal bridge contouring and nasolabial fold augmentation and their resolutions with a combination of the procedures described above (Figures 4 and 5).

3.4 | Delayed presentation

Impending vascular compromise is not always recognized immediately, and some patients may present themselves more than 24 hours after the initial event. Treatment is still warranted as any attempt to increase vasodilation and reduce inflammation will improve the outcome. An aggressive therapy is required to re-establish new vessel formation and tissue oxygenation. In addition to the acute treatments



A female patient aged 34 years old with no skin pathologies or history of allergy was treated for correction of nasal bridge and skin of the columella with non-diluted CaHA. Injection was performed with a cannula 22G-70mm and a volume of 0.3 ml injected in nasal bridge and 0.2 ml in columella (A and B show patient before the procedure). A slight blanching in the upper lip area was observed after the procedure. The patient did not report any pain but had received local anesthesia. A reticulate livedo and cyanosis in the upper lip was observed 2 h after the procedure (C and D). The patient was diagnosed with embolism of one of the branches of the upper labial artery. The patient received hyaluronidase injection 1500 IU at a standard dilution of 2 ml of 0.9% NaCl solution and sildenafil 100 mg. The following day the patient complained of swelling, reduced sensitivity of the upper lip and blueness in this area (E). A further dose of sildenafil 100 mg was prescribed. On the third day after the procedure the patient complained of burning mucosa, increasing swelling, decreased activity of the lip, and numbness of the tip of the nose (F–H). Taking into account the negative dynamics, the following treatments were assigned: hyperbaric oxygen therapy (1 procedure lasting 30 min); hyaluronidase 1500 IU injections in the columella and upper lip (0.5 ml); intravenous infusion of pentoxifylline 400 mg per 250 ml of 0.9% NaCl solution for 1 h; dexamethasone intramuscular injection 12 mg; *Solcoseryl*® gel on the lip mucosa; and sildenafil 100 mg once daily. On the fourth day after the procedure the patients dynamics were more positive. The skin of the upper lip was pale pink, and swelling had decreased (I). The treatments above were repeated on days 4 and 5 after which the lip had greatly reduced in volume, skin was light pink in color, the mucosa was restored to its pink coloring, and numbness of the lips had decreased (J). The patient was actively observed for 2 weeks until there was complete resolution of the signs of ischemia

FIGURE 5 Case report documenting the development of necrosis following injection of CaHA for nasal bridge contouring and its resolution. Courtesy of Professor Yana Yutskovskaya

highlighted in Figure 3, patients should receive daily hyperbaric oxygen therapy sessions for 1-2 weeks. PRP therapy may need to be continued weekly for several weeks to improve skin texture and to soften the edge between the damaged and undamaged areas. At later stages, this may be combined with microneedling, or laser therapy. Meticulous wound care including regular wound cleansing and gentle debridement of the necrotic tissue is essential to reduce healing time and limit scar formation.

3.5 | Treatment of open wounds

The presence of necrotic tissue in a wound is a physical impediment to healing and a medium for bacterial growth. If dried serum or other debris is present, it should be removed and clearly necrotic tissue debrided. Debridement should be conservative never removing questionable tissue as the final outcome is generally better than anticipated (Figure 3). Consensus was not achieved on the type of antibiotic. Some members felt therapy should be instituted with an agent that is of benefit for its anti-inflammatory effects as well as to prevent secondary infection, such as a tetracycline (eg, doxycycline), and others that one with a strong antimicrobial action was required such as ciprofloxacin. Yet others believed antibiotics should only be prescribed if there are severe signs of necrosis. If therapy is initiated, a switch to another antibiotic may be required after culture results. In addition to regular debridement of necrotic tissue, routine wound care should involve adequate hydration, daily dressings, and monitoring for secondary infection. These steps could be performed in conjunction with hyperbaric oxygen therapy once or twice daily to improve ischemia and reduce tissue loss. Open therapy with a bland ointment may be preferable initially as it allows daily cleaning of the wound with running water. Specialized dressings, such as those made of soft silicone film (eg, Mepitel Film) or hydrocolloid gel sheets (eg, DuoDERM), maintain a moist environment and support autolytic debridement and can be changed every 2 days. They are designed to protect fragile and sensitive skin and minimize risk of skin breakdown and should be applied until re-epithelialization is complete. Care must be taken with closed dressings to avoid the risk of superinfection.

For open wounds that are not healing properly, PRP therapy may be useful for bringing a higher concentration of platelets to the wound site and fighting infection. Some case reports have described success with adipose-derived stem cell therapy harvested from each patient's abdominal subcutaneous tissue for treating skin necrosis after filler injection.[73,74]

3.6 | Treatment of closed wounds

Due to the replacement of normal tissues by fibrous material, the healing process may result in scar formation in spite of debridement and aggressive dressing changes. Scars often cause contracture and subsequent cosmetic disfigurement, which results in a traumatic burden to the patient. Dressings that keep the wound moist should continue to be used until it is completely healed. A number of different types of lasers have been used to improve scar appearance including: pulsed dye laser, nonablative fractionated laser resurfacing, and fractionated laser resurfacing.[66]

Microneedling (collagen induction therapy) may be considered to improve healing and reduce scar formation. This technique uses fine needles to puncture the skin at various depths to create a controlled skin injury without damaging the epidermis.[75] Each puncture creates a channel in the dermis that stimulates the release of growth factors and cytokines. In turn, these stimulate new collagen and elastin production along with angiogenesis. A number of automated microneedling devices are available including dermal rollers and the more recently developed dermal stamps or pens. Microneedling can also be combined with other treatments including growth factors, vitamin C, and PRP to enhance its skin rejuvenation properties. It is recommended to repeat treatment at 4-week intervals. Patients should be advised that the full cycle of collagen production is a slow, multistage process that can take up to 10 months to achieve final results.

4 | DISCUSSION AND FURTHER CONSIDERATIONS

In this document, a group of international physicians with expertise in the treatment of dermal filler complications collaborated to develop a consensus on the management of vascular compromise following treatment with CaHA based on their collective clinical experience and the published literature. Although it remains rare, all physicians should be equipped to recognize and manage this event either as a result of a treatment performed in their own practice, or when dealing with patients referred to them for an adverse event resulting from a treatment elsewhere. The availability or doses of some of the treatments outlined in this consensus may vary by country, and while the consensus document outlines the key steps to follow, treatments may have to be adapted to what is locally available. What is essential is that diagnosis is rapid and treatment is initiated immediately.

While massage is generally recommended as one of the first steps following accidental intra-arterial injection to encourage blood flow and remove any obstruction, consensus members warned that consideration should be given to the volume of injectate. With volumes of CaHA <0.1 mL, distribution over a larger capillary network and into the venous system is likely to be beneficial. However, massage of bolus volumes greater than this might distribute the embolus over a larger capillary network increasing the area of compromised tissue. Therefore, as a preventative precaution, consensus members advise to limit bolus injection to 0.1 mL. If boluses of >0.1 mL were injected into an artery, massage should be delayed until treatments to dilate arteries have been administered.

Hyaluronidase is recommended for impending vascular compromise regardless of whether an HA or CaHA filler was used because

of its edema-reducing properties, effects on capillary permeability, and anti-inflammatory properties, all of which combine to increase blood flow to the affected area and promote wound healing. While large volumes of hyaluronidase could also increase pressure on the tissue, consensus members believe that in reality this would be very limited and lymphatic drainage would remove most of the additional fluid from the affected area.

5 | CONCLUSIONS

With this manuscript, the authors address the need for an expert consensus on the management of vascular occlusions following inadvertent intra-arterial injection of CaHA. Avoiding and treating vascular compromise require a detailed understanding of facial anatomy. Early recognition of vascular occlusion and rapid and aggressive treatment are required to avoid irreversible changes. All physicians performing these injections should have a well-stocked supply of recommended medication, treatment options, and devices for impending necrosis or vision loss. The availability of an up-to-date, office-based protocol for the prevention and treatment of vascular-related complications is essential for the timely and effective resolution of complications.

ORCID

Jani van Loghem https://orcid.org/0000-0001-6720-7434
Jonathan Kadouch https://orcid.org/0000-0001-5543-5675

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