

Treatment Algorithm for Hyaluronic Acid-Related Complication Based on a Systematic Review of Case Reports, Case Series, and Clinical Experience

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Abstract

Study Design: Systematic review of hyaluronic acid (HA)-related complications.

Objective: To systematically review all available literature including case reports and case series to identify a pattern for the management of vascular compromise resulting in facial skin ischemia and ocular manifestations following HA injection.

Methods: This review was based on a systematic search of 3 electronic databases PubMed, CINAHL, and Scopus for all available literature including case series and case reports from database inception to July 2019. Only a total of 52 case reports/series were eligible for review and included 107 patients.

Results: The reviewed literature available was comprised from case reports/series and indicated that management of both impending skin necrosis and visual disturbances is variable with no repetitive pattern of action. Yet, successful management is time dependent as early interventions stopped progression and, in some cases, even reversed adverse effects.

Conclusion: Results found no universal protocol for achieving optimal results for adverse effects and as such, we present a step-by-step algorithm for the emergency management of complications following HA injection.

Keywords

hyaluronic acid, complications, treatment algorithm, systematic review

Introduction

Soft tissue filler injections are one of the most popular non-surgical facial rejuvenation procedures, among which, hyaluronic acid (HA) is most commonly used. Although HA has a high safety profile, there can be complications, especially when injected by inexperienced physicians or unqualified “injectors.”¹ Common complications such as superficial or uneven placements of filler material and granulomatous reactions can be managed in private office/clinic settings. Other complications experienced within 24/48 hours post-injection, although rare, may lead to devastating results and require immediate intervention in emergency room (ER) in the first hours or minutes post-injection. These include vascular compromise resulting in skin necrosis, visual loss, and nerve damage as well as infections that cannot be managed with oral antibiotics alone.²⁻⁶

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At the Sheba Medical Center, Israel, the majority of cases seen are late presentations. However, few cases may benefit from a fast and efficient intervention. Protocols for the management of HA injection-related complications have been previously proposed.⁵⁻¹⁰ Yet, a fast, simplified, step-by-step algorithm for emergency situations is required for ER physicians, who need to effectively manage these acute complications, in which any further delay of treatment may result in significant facial deformity or blindness. Therefore, the purpose of this review is to systematically evaluate case reports and case series to identify a pattern for the management of vascular compromise resulting in facial skin ischemia and ocular manifestations following HA injection based on available peer reviewed literature.

Methods

A systematic and rigorous search across the electronic health databases PubMed, CINAHL, and Scopus was conducted from database inception to July 2019. Boolean connectors AND/OR were used to combine indexed/MeSH terms and keywords including hyaluronic acid OR hyaluronoglucosaminidase OR hyaluronidase AND cosmetic techniques OR injections, subcutaneous OR dermal fillers AND embolism OR ischemia OR complication* OR occlusion OR optic neuropathy OR blindness. The reference lists of all included cases studies/series were reviewed to identify any potential cases not captured through the initial search strategy and when possible, full-text articles were retrieved.

Inclusion and Exclusion Criteria

The search criteria for this review incorporated peer-reviewed case reports/series published in English that described facial skin ischemia or ocular manifestations after injecting solely HA with detailed description of the management conducted to reverse the adverse event and final outcomes. The authors did not impose any parameters concerning the year of publication in order to capture the depth and breadth of data. Editorials, reviews, conference proceedings, animal studies, cadaveric experimental and theoretical approaches, and case reports and case series presenting skin or vascular compromise without full description of the management and final outcomes were excluded.

Data Evaluation and Extraction

A total of 669 references were downloaded into EndNote X8. After duplicates were removed, the search strategy identified 502 prospective papers (Figure 1). Authors UA and MH identified 51 potential papers through the evaluation of titles and abstracts, 1 additional report was found by reviewing reference lists of included studies. Altogether 35 papers described vascular ischemic events resulting in skin

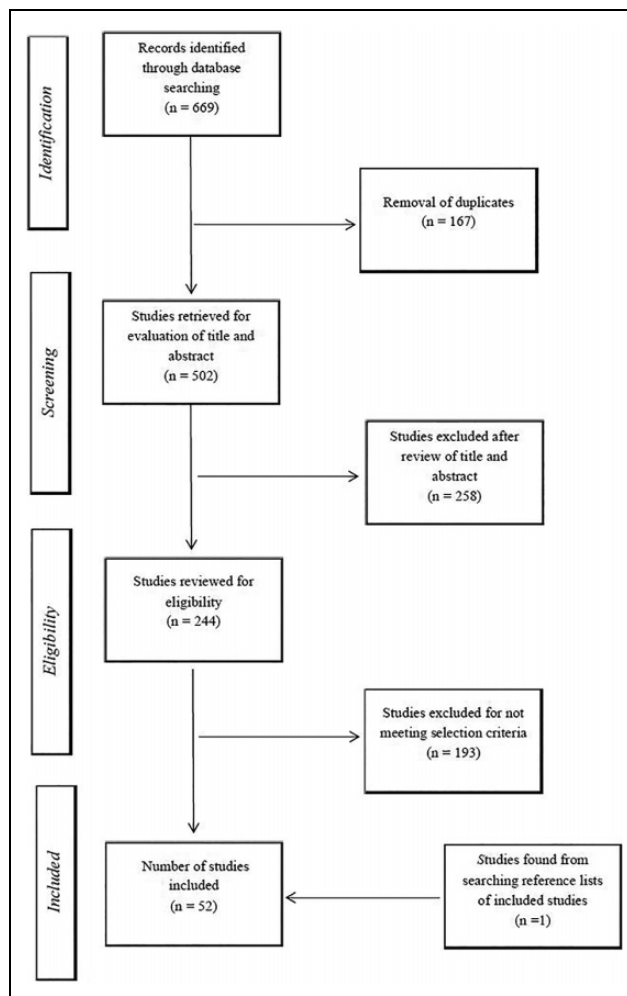


Figure 1. Decision trail of included studies.

necrosis and 17 papers described ophthalmic complications resulting in vision disturbance or orbital dysfunction. Based on the inclusion criteria, authors UA and MH independently reviewed all included papers. Any disparities were resolved by means of collegial discussion until consensus was reached.

A total of 52 case studies/series were systematically summarized and synthesized. Findings were reviewed and are presented as 2 key domains: vascular compromise with impending skin necrosis following HA injection and management and vascular compromise with ophthalmic vascular obstruction following HA injection and management. Data extracted included author(s), year of publication, country of origin, number of patients, gender, age, area of injection, vascular territory affected, timing of initial treatment, number of hyaluronidase injections and timing from event, quantity injected and technique of injection, topical and systemic treatment other than hyaluronidase, ocular manifestation and other neurological signs and symptoms, end point of acute event and final outcomes (Tables 1 to 4).

In addition, this review is informed by our clinical experience and in support we present 2 exemplars. Participants

Table 1. Isolated Reports of Vascular Compromise With Impending Skin Necrosis Following HA Injection and Management.

Year, country	Number of patients, gender (F/M), age	Area of injection ^a	Timing of initial treatment	No. of hyaluronidase injections	Hyaluronidase injection dosage	Hyaluronidase injection technique	Additional treatment	Surveillance period and outcomes
2002-2018	25 (23 F, 2 M) 22-57 years	NLF—8 pts Nose—6 pts Glabella—5 pts Temple—2 pts Forehead—2 pts.	Immediate to 9 days (216 hours)	13/25 pts 1-4 impulses 1 injection—7 pts 2 injections—1 pt 3 injections—2 pts 4 injections—1 pt Unknown—2 pts	15-1500 U per impulse (max. 4000 U for 1 pt)	Not specified—4 pts Injection into and beyond involved area—3 pts Into ischemic area—2 pts Along arterial distribution course—2 pts Multiple points around linear erythema—1 pt US guided—1 pt	Topical and intralesional: Antibiotics Cold compresses Collagenase-antibiotic ointment Diligent moisturized wound care and daily dressings Disinfection with iodophor Epidermal growth factor gel Hydrogen peroxide Minoxidil spray (vasodilation) Nitroglycerin (paste and sublingual) Platelet-rich plasma (intradermal) Recombinant bovine basic fibroblasts growth factor gel Saline soaking Vaseline gauze dressing Warm compresses Systemic: Antibiotics Aspirin Enoxaparin Intradermal lidocaine Intravenous prostaglandin E1 Intravenous urokinase NSAIDs Steroids Valacyclovir Vasodilators Others: 833-nm light emitting diode irradiation Carbon dioxide laser Hyperbaric oxygen therapy Surgical intervention	24 hours—300 days Full recovery—10 pts Hyperpigmentation, erythema, telangiectasia, superficial erosions, minimal scarring, minimal asymmetry—11 pts Prominent scarring—2 pts Surgical intervention for debridement (1 with skin grafting)—2 pts Temporary hearing loss that later resolved—1 pt

Abbreviations: B-FGF, basic fibroblast growth factor; EGF, epidermal growth factor; F, female; HA, hyaluronic acid; He-Ne laser, helium-neon laser; M, male; NLF, nasolabial fold; nm, nanometer; NSAIDs, nonsteroidal anti-inflammatory drugs; PRP, platelet-rich plasma; Pt, patient; Pts, patients; U, Units; US, ultrasound.
^aTotal number can exceed the sum of all patients as more than 1 region was injected with HA.

Table 2. Case Series of Vascular Compromise With Impending Skin Necrosis Following HA Injection and Management.

Author (year) Country	Number of patients, gender (F/M), age	Injection sites ^a	Timing of initial treatment after filler injection	No. of hyaluronidase injections	Hyaluronidase injection dosage	Hyaluronidase injection technique	Additional treatment	Surveillance period and outcomes
Wang ³⁴ (2018) China	2, F 24, 42 years	Chin—2 pts	6 hours 24 hours	Time and number of impulses unknown—2 pts	Amount and dosage unknown—I pt 100 U—I pt	Not specified—I pt Multipoint injection—I pt	Topical: Hot compresses Topical EGF gel	3-9 days Superficial ulcers development—I pt Swelled and discolored tongue, mild atrophy of right side of tongue, paresthesia—I pt 3-30 days Full recovery—2 pts Hyperpigmentation, minimal scarring—2 pts
Robati ³⁵ (2018) Iran	4 ^b , F, 29-52 years	NLF—2 pts Lips—2 pts	Immediate to 8 days	1 injection—all 4 pts	100-300 U	Not specified	Topical and intralesional: Intralesional steroids (Triamcinolone) Nitroglycerin paste Systemic: Acyclovir Antibiotic Aspirin Others: Low-level laser treatment	3-30 days Full recovery—2 pts Hyperpigmentation, minimal scarring—2 pts
Zhang ³⁶ (2018) China	9, F 20-35 years	NLF—5 pts Alar groove—I pt Glabella—I pt Forehead—I pt Lips—I pt	Not reported	1 st—0 time—on admission between 5 minutes to 3 days Number of impulses not known	Amount and technique unknown	Areas of injection of HA and areas of skin ischemia	Topical and intralesional: Local cooling with antibiotics saline soaked gauze (4°C) Nitroglycerin paste Systemic: Antibiotics Steroids Others: Hyperbaric oxygen therapy	5-7 days Full recovery—8 pts Significant local skin damage and scarring—I pt
Ciancio ³⁷ (2018) Italy	2, F 36, 45 years	NLF—2 pts	3 days—2 pts	5 injections—I pt 6 injections—I pt	40 U per cm ² —2 pts Total amount unknown	Deep dermal plane Distributed over the treated area through microinjections	Topical and intralesional: Nitric oxide paste Warm compresses Systemic: Antibiotics Aspirin Steroids	45 days Full recovery—2 pts
Hong ³⁸ (2017) South Korea	2 ^b , F 32, 27 years	NLF—2 pts	1 day—I pt 4 days—I pt	2 injections—2 pts	Amount and technique unknown (the author mentions a "second" injection of 1500 U)	Not specified	Topical and intralesional:	6 weeks-3 months Complete resolution—I pt Depressed scar and asymmetric nostrils—I pt

(continued)

Table 2. (continued)

Author (year) Country	Number of patients, gender (F/M), age	Injection sites ^a	Timing of initial treatment after filler injection	No. of hyaluronidase injections	Hyaluronidase injection dosage	Hyaluronidase injection technique	Additional treatment	Surveillance period and outcomes
Andre ³⁹ (2015) France	5 ^b , F, 30-42 years	NLF—3 pts Nose (tip)—1 pt Lip—1 pt	Immediate—72 hours	1 injection—2 pts Not administered—3 pts	Amount unknown	Along vascular territory distribution—I pt Not specified—I pt	Potassium permanganate soaking Pustule extraction with forceps Saline soaking Vaseline gauze dressing Systemic: Antibiotics Aspirin Nitroglycerin (sublingual) Others: 833-nm LED irradiation Hyperbaric oxygen therapy Topical: Antiseptic solution Cream Local massage Systemic: Aspirin Others: Pulse-dye laser Topical and intralesional: Magnesium application Systemic: Anti-inflammatory agents Antibiotics Aspirin Papaverine (intramuscular) Others: Hyperbaric oxygen therapy Infra-red irradiation	7-30 days Full recovery—3 pts Hyperpigmentation—I pt Skin necrosis—I pt
Sun ⁴⁰ (2015) China	20, 19 F, 1 M 21-52 years	Nose—15 pts NLF—6 pt	Not reported	18/20 pts Number of impulses unknown	150 U	Not specified	5 days Full recovery—I 3 pts Skin necrosis and subsequent scarring and vestibule deformity—7 pts	

(continued)

Table 2. (continued)

Author (year) Country	Number of patients, gender (F/M), age	Injection sites ^a	Timing of initial treatment after filler injection	No. of hyaluronidase injections	Hyaluronidase injection dosage	Hyaluronidase injection technique	Additional treatment	Surveillance period and outcomes
Bravo ⁴¹ (2015) Brazil	3 (2 F, 1 M) 52, 61 (2 pts) years	NLF—2 pts Cheek—1 pt	30 hours—1 pt Not reported—2 pts	3 injections—1 pt Time and number of impulses unknown—2 pts	160 U—1 pt 225 U—1 pt 500 U—1 pt	Not specified	Topical and intralesional: Warm compresses Systemic: Antibiotics Aspirin Clonidogrel Enoxaparin Sildenafil Steroids Vasodilators Others: Hyperbaric oxygen therapy Topical and intralesional: Saline (warm) soaking Systemic: Antibiotics Aspirin Steroids Others: He-Ne laser	5 days—1 pt Unknown—2 pts Complete resolution—1 pt Discrete atrophic scars—2 pts
Lee ⁴² (2015) South Korea	2 ^b , F 28, 42 years	NLF—1 pt Nose—1 pt	3 hours—1 pt 3 days—1 pt	Number of injections unknown—2 pts	Amount not known	Not specified	Topical and intralesional: Saline (warm) soaking Systemic: Antibiotics Aspirin Steroids Others: He-Ne laser	10 days—4 weeks Full recovery—1 pt Minimal scarring—1 pt
Grunebaum ⁴³ (2009) USA	3 (2 F, 1 M) 25, 38, 42 years	NLF—2 pts Nose (tip)—1 pt	Immediate—3 days	4 injections—1 pt 1 injection—1 pt Not administered—1 pt	40 U—1 pt Unknown—1 pt	Not specified	Topical and intralesional: Antibiotics Collagen injection (for structural support) Hydrocolloid dressing Nitroglycerin paste Triamcinolone Systemic: Antibiotics Others: Later debridement	Surveillance period not reported Full recovery—2 pts Scar and mild asymmetry (vestibular)—1 pt

Abbreviations: B-FGF, basic fibroblast growth factor; EGF, epidermal growth factor, F, female; HA, hyaluronic acid; He-Ne laser, helium–neon laser; M, male; NLF, nasolabial fold; nm, nanometer; NSAIDs, nonsteroidal anti-inflammatory drugs; Pt, patient; Pts, patients; U, Units.

^aTotal number can exceed number of patients as more than 1 region was injected with HA.

^bMore cases were present in the original report but omitted due to nonvascular complications, filler other than purely HA, no intervention performed or insufficient information.

Table 3. Isolated Reported Cases of Vascular Compromise With Ophthalmic Vascular Obstruction Following HA Injection and Management.

Year, country	Number of patients, gender (F/M), age	Area of injection ^a	Ocular manifestation and other neurological signs and symptoms	Ophthalmic Vessels and nerves involved	Timing of initial treatment	Hyaluronidase injection dosage	Hyaluronidase injection technique	Additional treatment	Outcomes
2006-2019 China, Germany, Malaysia, South Korea, Taiwan, USA ^{4,44-55}	13 (10 F, 3 M) 20-52 years	Nose—10 pts (5/10 into dorsum of nose, 2/10 into tip, 3/10 unspecified) Glabella—6 pts Forehead—2 pts Cheek/midface—1 pt	Complete vision loss—7 pts (right—6, left—1) Partial vision loss—4 pts (right—2, left—1, side unspecified—1) Restricted eye movements—7 pts Blepharoptosis—3 pts (2—right, 1—left) Diplopia—3 pts Upper motor neuron signs—2 pts (1 subjective only)	Ophthalmic a.—5 pts Retinal a.—7 pts Posterior ciliary a.—1 pt Middle cerebral a.—1 pt (right) Oculomotor n.—5 pts Optic n.—2 pts Trochlear n.—1 pt	Immediate to 7 hours (in 6 cases timing was not emphasized)	60-1800 U 5 pts did not receive hyaluronidase	Subcutaneous—6 pts Retrolbulbar—3 pts In vicinity of supraorbital and infraorbital vessels—1 pt IATT—1 pt	Topical: Antibiotics Epidermal growth factor Heat packs Massage Steroids Timolol maleate Vasodilators Systemic: Acetazolamide Antibiotics Aspirin Dextran Fluids Methylcobalamin (neuro-nutrition) Pentoxifylline Steroids tPA Urokinase—IATT Vasodilators Others: Hyperbaric oxygen therapy Low-level laser therapy Oxygen 1 pt emergency decompressive craniectomy (due to right ICH, SAH and midline shifting)	End of surveillance period— from 25 days to 1 year No improvement—5 pts Partial resolution of symptoms—4 pts Complete resolution of symptoms—4 pts (1 pt complete resolution of symptoms from complete vision loss)

Abbreviations: F, female; HA, hyaluronic acid; IATT, intra-arterial thrombolytic therapy; ICH, intra-cerebral hemorrhage; M, male; Pt, patient; Pts, patients; SAH, subarachnoid hemorrhage; tPA, tissue plasminogen activator; U, Units.

^aTotal number can exceed number of patients as more than 1 region was injected with HA.

Table 4. Case Series Vascular Compromise With Ophthalmic Vascular Obstruction Following HA Injection and Management.

Author (year) Country	Number of patients, Gender (F/ M), age	Area of injection ^a	Ocular manifestation and other neurological signs and symptoms	Distribution of skin ischemia	Ophthalmic Vessels and nerves involved	Timing of initial treatment	Hyaluronidase injection dosage ^a	Hyaluronidase injection technique	Additional treatment	Outcomes
Zhang ⁵⁶ (2019) China	3, F 23, 35, 37 years	Glabella—2 pts Nose—1 pt Forehead— 1 pt	Complete vision loss—1 pt (left) Partial vision loss—2 pts (right) Restricted eye movements—1 pt Blepharoptosis—3 pts Diplopia—1 pt	Not specified	Retinal a.—2 pts Posterior ciliary a.—3 pts	Immediate to 4 hours after injection	1500 U—2 pts (as a second injection) Amount unknown—3 pts	Subcutaneous—3 pts Retrobulbar—2 pts	Systemic: Anti-aggregant Glucocorticoids vasodilators Others: Hyperbaric oxygen	End of surveillance period—from 6 months to 12 months No improvement— 3 pts
Thanasarnaksorn ⁵⁷ (2018) Thailand	6 (5 F, 1 M) 23-61 years	Nose—4 pts Temple—1 pt Forehead— 1 pt	Complete vision loss—2 pts (right eye) Partial vision loss—4 pts (right—1, left—3, 2 pts had only light perception) Restricted eye movements—3 pts Blepharoptosis—4 pts Pain—4 pts Headache—3 pts Nausea—2 pts Multifocal acute brain infarction—1 pt Subacute brain infarct—1 pt	Nose—2 pts Glabella—2 pts Forehead—2 pts Not specified— 3 pts	Ophthalmic a.—2 pts Retinal artery—3 pts Choroidal—1 pt Oculomotor nerve—2 pts Optic nerve—1 pt	Immediate to 72 hours after injection	300-1500 U (maximal cumulative dose more than 2500 U for patient)	Subcutaneous—6 pts Retrobulbar—2 pts Periorbital—1 pt (around and within supratrochlear notch)	Topical: Antibiotics Ocular massage Steroids Pressure decreasing eye drops Nitroglycerin transdermal pad (chest) Systemic: Anti-aggregants Antibiotics Antiepileptic drugs Diuretics Steroids Parecoxib Metoclopramide Others: Hyperbaric oxygen Low-level laser therapy Anterior chamber paracentesis Rebreathing into plastic bag (vasodilation) Carbogen inhalants Pulse electromagnetic frequency	End of surveillance period—24 hours to 6 months Partial resolution of symptoms—4 pts ^c Complete resolution of symptoms—2 pts 1 pt received artificial eye
Zhu ⁵⁸ (2017) China	4, F 23-35 years	Nose—3 pts Forehead— 1 pt	Complete vision loss—4 pts (right—1, left—3) Blepharoptosis—4 pts	Not specified	Ophthalmic a.—1 pt Retinal artery—2 pts	4-34 hours	1500-3000 U (maximal cumulative dose 6000 U for 1 pt)	Retrobulbar—4 pts	Topical: Timolol Massage Systemic: Acetazolamide Aspirin	End of surveillance period—3-8 weeks No improvement— 3 pts

(continued)

Table 4. (continued)

Author (year) Country	Number of patients, Gender (F/ M), age	Ocular manifestation and other neurological signs and symptoms	Distribution of skin ischemia	Ophthalmic Vessels and nerves involved	Timing of initial treatment	Hyaluronidase injection dosage ^a	Hyaluronidase injection technique	Additional treatment	Outcomes
				Choroidal- oculomotor nerve—2 pts Optic nerve—2 pts				Mannitol Nitroglycerin Steroids Others: Anterior chamber paracentesis Hyperbaric oxygen therapy	Partial resolution of symptoms—I pt
Kim ⁵⁹ (2015) South Korea	4 ^b , F 24–41 years	Nose and glabella— apply for all pts	Nose and glabella— all pts	Ophthalmic a.—all pts	Immediate to 5 hours	1000–9000 U Amount unknown—I pt	Subcutaneous—I pt IATT—4 pts	Systemic: IATT—urokinase	No improvement— all pts

Abbreviations: F, female; HA, hyaluronic acid; He-Ne Laser, helium-neon laser; IATT, intra-arterial thrombolytic therapy; M-male; Pt, patient; Pts, patients; tPA, tissue plasminogen activator; U, Units.

^aTotal number can exceed number of patients as more than 1 region was injected with HA or more than 1 hyaluronidase injection was performed

^bMore cases were present in the original report but omitted due to nonvascular complications, filler other than purely HA, no intervention performed or insufficient information

Improved ocular movements and resolution of ptosis, but partial or complete vision loss was persistent

provided informed consent for the use of digital photography for the purposes of treatment, teaching, and use in academic publications. In the following Results section, we also suggest a treatment algorithm that incorporates our clinical experience and the case reports/series findings.

Results

Characteristics of Included Studies

This systematic review of HA-related complications included 52 studies published from 2002 to 2019. Studies were conducted across 15 countries, including Asia: Malaysia, China, South Korea, Japan, Taiwan, Thailand, Singapore, and Indonesia; Europe: Italy, France, Greece, and Germany; Middle East: Iran; and The Americas: USA and Brazil (see Tables 1 to 4).

The total number of patients experiencing HA-related complications across the studies was 107 with a mean age of 35.26 years. Ninety-eight were female with a mean age of 34.9 years, ranging from 20 to 61 years. Nine patients were male with a mean age of 38.16 years, ranging from 23 to 61 years.

Non-Ophthalmic-Related Vascular Obstruction

Clinically, tissue ischemia developing immediately after injection is characterized by sudden onset of pain accompanied by regional skin discoloration, prolonged regional capillary refill time, livedo reticularis, and later blistering, skin necrosis and late scarring. Delayed-onset tissue ischemia starting few hours after injection was reported as well, this late presentation is probably the result of embolic downstream propagation by spontaneous dislodgment from the primary obstructed location or secondary to manipulation, that in its new location blocks collaterals that were previously functional.^{60,61}

Tissue ischemia can result directly or indirectly. A direct ischemia is caused by intra-vascular injection of filler material into a blood vessel and blocking a terminal vessel, another cause of tissue ischemia in this setting can be direct needle injury to the vessel.⁶² An indirect ischemia is probably the cause of a compressed blood vessel secondary to juxta-arterial injection of hygroscopic HA which increases interstitial pressure around the blood vessel (area of minimal distensibility of skin such as lower third of nose). A combination of all the abovementioned mechanisms of tissue ischemia is also possible.^{2,11} Injection-related skin necrosis can involve a small and specific area of the skin but can also correspond with the entire territory supplied by the artery involved and even several territories.⁶¹

In the case of intra-arterial injection against flow direction with high enough pressure to overcome the systolic blood pressure inside the artery, filler can momentarily move in retrograde fashion before branching point, then propagate with blood flow to an artery that was not

primarily involved in a separate territory, forming a so-called paradoxical embolus. This can also explain reports of ophthalmologic complication during injections to the nose and glabellar area. Another mechanism that can explain the latter is passage of filler material through arterial-venous anastomoses.^{4,44}

Tables 1 and 2 show no consistent pattern for the management of skin ischemia with authors presenting a personal armamentarium for coping with the situation, and with good results. The high success rate for managing skin ischemia (unlike ophthalmic vascular obstruction) may be explained by different causes, including good basic knowledge of possible treatment strategies, as well as the abundant facial blood supply and compensation of ischemic areas by neighboring angiosomes as already described by Taylor et al.⁶³

Proposed Algorithm

Based on the limited literature, and informed by our experience, we present an algorithm for the emergency management of complications following HA injection (Figure 2).

In our algorithm (Figure 2), if skin ischemia is suspected, aspirin or any alternative anti-aggregant should be administered immediately for the treatment and prevention of blood clot formation secondary to stasis proximal to the obstruction point. While the patient is receiving high dose aspirin, hyaluronidase should be obtained. Frequently, patients are referred to the emergency department with hyaluronidase ampule for further treatment, but hospital's pharmacies also hold hyaluronidase for different purposes. The injection dose and technique recommendations regarding hyaluronidase use has changed in the last decade. The older reports advocated injection of few dozens of units subcutaneously along the distribution of the arteries involved. The latest approach is to "flood" the skin territories of tissue ischemia with hundreds of units in deep and superficial planes including 1 cm beyond the area of involvement, thus degrading extraluminal obstruction and penetrating the blood lumen's vessel as well.⁶⁰ Dilution of hyaluronidase should be undertaken in 10 cc of normal saline or water for injection and then injected with 1 cc syringes using a 25-30 Gauge needle. Immediate subjective and objective results after injection are expected. Hourly follow-up is recommended and if necessary, repeated injection in 60 minutes interval for at least 4 hours is recommended.⁶¹ A facial oxygen mask should also be administered.

Hyaluronidase is not free of side effects, yet, the incidence of adverse reactions is considered to be low. Local skin reactions are the most common. Mild allergic reactions such as urticaria and angioedema occur in less than 0.1% of cases, and anaphylactic reactions have been documented as well.^{2,5,64,65} It should be emphasized that in the authors' opinion, the low probability of hyaluronidase' adverse effects, especially in hospital settings where immediate

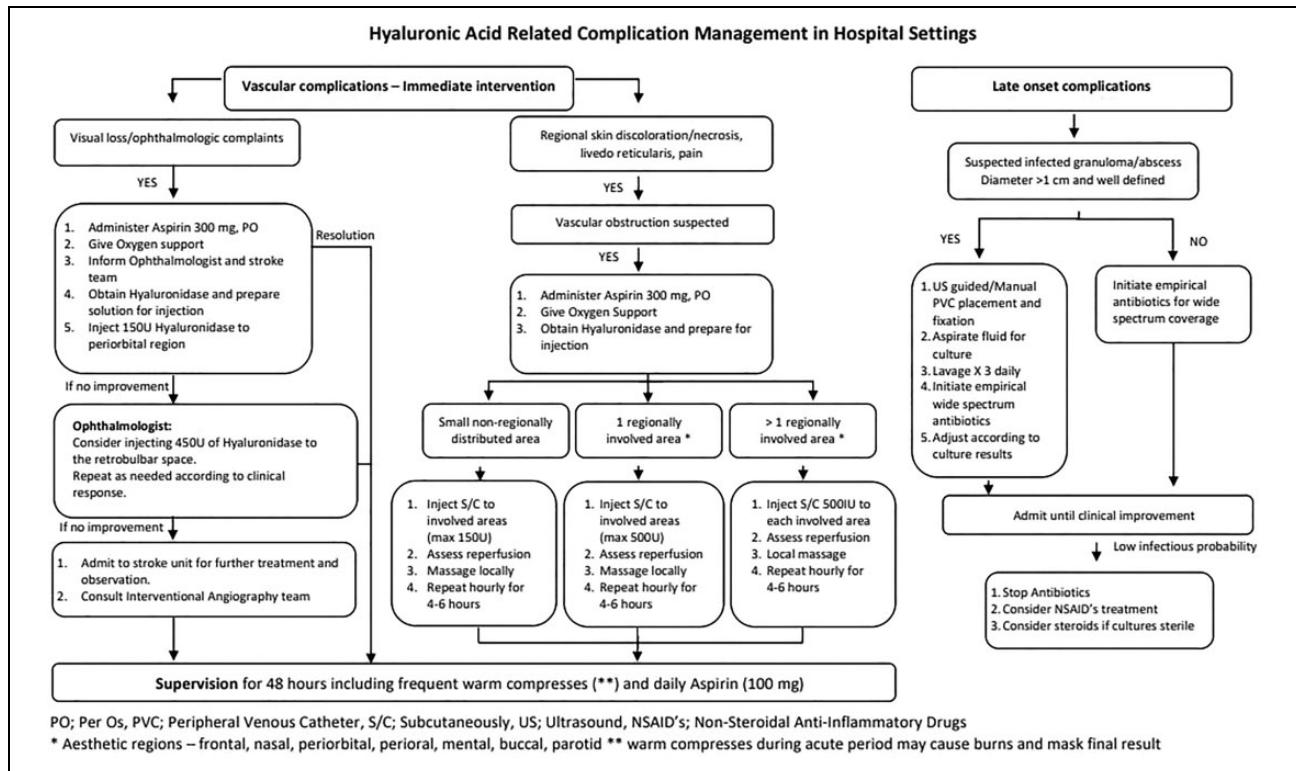


Figure 2. Hyaluronic acid-related complication management in hospital settings.

treatment is available, makes withholding its use unjustified in emergency cases to allow tissue salvage. Albeit the patient's informed consent is required.

Other local and systemic treatments have been suggested.^{7,11,12,40} It is our belief that application of warm compresses in the emergency setting should be performed with caution, as continuous exposure to hot objects, may induce thermal burns and mask skin changes after the introduction of hyaluronidase, especially if local anesthetics were combined with the filler. Topical nitroglycerin paste or a patch over involved skin to achieve local vasodilation is advised, although its use should be when the patient is in a supine position. Furthermore, local and systemic antibiotics and anti-herpetic therapy, in our opinion, are not necessary in the acute management.

Ophthalmic Vascular Obstruction

The privilege of a 6-9-hour window for treating skin ischemia after filler injection is absent in the case of ophthalmic complications. In this case, retinal necrosis and visual loss may become irreversible 90 minutes after the onset of symptoms. Therefore, an immediate intervention is required in such cases, especially when considering the time until arrival to the ER.^{9,45} It should be emphasized that ophthalmic compromise should be managed in a multi-disciplinary manner involving ophthalmologists, neurologists, and plastic surgeons who are familiar with the soft

tissue filler and injection techniques and thus can certify an effective intervention.

High-level evidence is lacking for management (Tables 3 and 4), yet, limited reports of improvement of visual acuity after complete and partial vision loss secondary to filler injection exist.^{4,45-50,57} A consensus opinion regarding the treatment of visual loss secondary to aesthetic intervention was recently published, suggesting a combination therapy using several retinal arterial vasodilators as well as anterior chamber paracentesis to decrease intra-ocular pressure.⁹ Regarding hyaluronidase, although the level of evidence is low, if administration is to be performed, repeated injections in peribulbar approach is considered to be safer than retrobulbar injection. A combination of subcutaneous hyaluronidase and intravenous urokinase for the management of HA-related arterial embolism has been suggested.^{9,13,51}

The approach for the ophthalmic ischemic event is similar to the non-ophthalmic approach. This includes aspirin treatment and retrobulbar or peribulbar "flooding" with hyaluronidase in the vicinity of the ophthalmic artery and branches. The concept of flooding consists of repeated injections until clinical improvement is achieved.^{45,61} Retrobulbar injection is a dangerous procedure and may further complicate the situation, this should be conducted by an ophthalmologist who is familiar with the procedure. Whether visual acuity has improved or not, the patient should be admitted to a stroke unit for further supervision. Additional treatments have been previously suggested,

these include diuretics, vasodilators, steroids, pressure decreasing eye drops, and hyperbaric oxygen. These however should not postpone any immediate intervention.^{4,45-47,52,57,66}

Abscesses and Infected Granulomas

Infection post filler injection can present as redness and soft tissue swelling, or as an abscess and a granulomatous reaction that usually appear in a later onset. Based on our clinical practice, we frequently see patients experiencing such infections seeking medical attention after failed conservative management with topical agents and oral antibiotics. Although immediate intervention for tissue salvage is not required, we noticed better results with patients admitted and treated in our ward.⁶⁷

Facial abscess can be diagnosed through physical examination or using an ultrasound device. In cases where the subcutaneous finding is large and well defined, our preferred method of treatment begins with drainage, sending the content for Gram stain, acid fast stain, and cultures including mycobacterium. Following, empiric antibiotic therapy with amoxicillin/clavulanic acid and fluoroquinolones is initiated. Drainage of facial abscesses can result in severe distortion and aesthetic damage, for this reason, our method of drainage consists of paracentesis using a 20 Gauge catheter. Introduction of the catheter can be performed manually or under ultrasound guidance. The catheter is fixated using regular tape and left in place. Later on, lavage with saline is performed through the catheter 3 times a day until clinical improvement is seen, and the aspirated content has decreased sufficiently. In many cases, the addition of nonsteroidal anti-inflammatory drugs has proven to be useful.

In the case that aspirated fluid culture results are negative, antibiotic therapy is ceased and a short course of oral corticosteroids is initiated. Although the literature does not demonstrate the benefit of steroid treatment, our experience points that this modality of therapy is beneficial, and thus has been added to our algorithm. For smaller and ill-defined findings, drainage is not an option, and cultures cannot be collected. Empirical antibiotic treatment is initiated and daily clinical evaluation guides further treatment.

Skin necrosis involving an area corresponding to a territory supplied by a certain artery is highlighted in our case presented in Figure 3 in which the distribution of skin ischemia followed ophthalmic artery branches. Figure 4 demonstrates the temporary fixation of a catheter for paracentesis and lavage of the content of an abscess.

Discussion

As cosmetic procedures involving HA are increasing in popularity, complication rates, including severe tissue damage, follows. The attending physician in the ER is now facing a new challenge, in which pending vascular



Figure 3. Tissue ischemia corresponding to arterial distribution. A 33-year-old female presenting 26 hours after injection of HA to dorsum of nose with complains of right eye blurry vision and periorbital pain that started during injection. Skin discoloration in partial right ophthalmic artery distribution: right supraorbital, supratrochlear and dorsal nasal arteries (as well as angular artery).



Figure 4. Temporary fixation of catheter into abscess pocket. This figure is an example of fixation of 18 Gauge catheter. A 40-year-old female presenting 2 weeks following injection of HA to bilateral nasolabial folds, several days following the injection the patient complained of pain and tenderness in the injection area and later swelling. Before admission to our center, patient was treated by oral antibiotics and local creams by the primary injector with no improvement.

compromises presenting after minor procedures in office setting can result in facial deformity and even disability if not addressed efficiently and without any delay, as time is limited for tissue salvage.⁴⁰ Identification of an acute event following a cosmetic procedure is essential as time is crucial.

Treating these challenging cases require a team approach involving plastic surgeons, neurologists,

ophthalmologists, and emergency medicine physicians. These medical professionals should familiarize themselves with the possible pathogenesis as well as the “vascular territories (angiosomes) concept” for the understanding and the management of such cases, hence clarification of an algorithm regarding proper treatment is required. We believe encouraging this approach will avoid delay of treatment and increase the probability for recovery. Medical staff should know where hyaluronidase is placed and if available, how to readily access.

The algorithm in Figure 2 presents a step-by-step approach for the management of HA injection complications: in case of patient presenting with ophthalmic complaints, anti-aggregant should be administered immediately (if not contraindicated). Contact the on-call ophthalmologist for further evaluation and possible intervention as well as the neurologist for neurologic evaluation, considering administration of tissue plasminogen activator or angiographic intervention and setting of placements in stroke unit. Order hyaluronidase from where it is stored and start injecting: 150 Units in the periorbital region and wait for immediate feedback from the patient, repeat as needed, if no improvement is noted, consider retrobulbar injection of 450 Units, wait for immediate feedback and repeat as needed. Whether successful or not, the patient should be under supervision for at least 48 hours after the salvage attempt.

In case of non-ophthalmic vascular obstruction observed, give anti-aggregant (if not contraindicated) and fix oxygen supplementation, order hyaluronidase from where it is stored and inject according to aesthetic region involved: for small non regionally distributed area inject 150 Units hyaluronidase into skin discoloration area in superficial and deep subcutaneous planes and the patient should be instructed to gently massage affected areas to facilitate local distribution of hyaluronidase through the ischemic area, dislodge thrombi or emboli and to increase blood flow. Afterward, wait for subjective and objective feedback and repeat accordingly every 1 hour for 4 subsequent hours. If a whole regional unit is involved (forehead, nasal, orbital, oral, mental, buccal, over parotid), “flood” the area with up to 500 Units hyaluronidase in both superficial and deep subcutaneous plane including 1 cm beyond the involved area and wait for feedback, repeat accordingly every hour for 4 subsequent hours. If more than 1 aesthetic unit is involved, “flood” each area with 500 Units hyaluronidase in superficial and deep subcutaneous planes including 1 cm beyond the involved area and wait for feedback. Again, repeat accordingly once hourly for 4 subsequent hours. Later admit the patient for further 48 hours supervision and start daily anti-aggregant therapy.

In case of suspected infected granuloma or abscess, assess the finding manually, if the diameter is more than 1 cm and well defined, place (manually or ultrasound guided) temporary 20 Gauge catheter into the pocket, fixate the catheter, aspirate the content and send for cultures. Start

empirical antibiotic treatment and perform daily lavage with saline (by injecting 3-5 cc of saline into the pocket, and immediate aspiration), assess turbidity each time. Non-steroidal anti-inflammatory drugs are to be considered as well. Follow fluid culture results and prescribe antibiotics accordingly. In case of negative cultures, stop antibiotics and consider a short course of oral steroids. In case the dimension of the finding is less than 1 cm, do not attempt to place a catheter, start immediately an empiric antibiotic trial and consider use of nonsteroidal anti-inflammatory drugs. Later, if probability of infection is low according to clinical evaluation and laboratory results, stop antibiotics and start a short course of oral steroids.

Hyaluronidase use for filler injection-related complications is still considered off-label. Hospitals' pharmacies hold hyaluronidase for other FDA and EU approved indication, such as hypodermoclysis, increased subcutaneous drug absorption, treatment of extravasation injury and subcutaneous urography.^{2,64} It is only recently that we have come to an understanding with the pharmacy in our institution that hyaluronidase should be supplied for plastic and reconstructive surgery purposes as well.

Vascular and ophthalmic complications following injection of HA are not common, and as demonstrated in Tables 1 to 4, no clear repetitive pattern of actions for the management of these events could be identified. It should also be kept in mind that many incidents of tissue ischemia involving a small skin territory may go unnoticed without the patient seeking medical attention or the injector diagnosing tissue ischemia.

Unlike skin necrosis, which may be managed by the injecting physician without admission, visual disturbances require urgent intervention in the hospital setting or by an experienced physician rather than the injector and cannot be managed “under the radar.” For this reason and the unique nature of the event, it is expected that these cases will be reported.

Vascular compromises of skin territories, in the majority of cases listed in Tables 1 and 2, resulted in complete or near complete recovery of ischemic signs. Out of 77 patients that experienced impending skin necrosis, 16 patients developed more than just minimal scarring and 3 patients eventually went through debridement, among which, areas debrided were nasal alae in 2 cases,^{14,43} and nasal dorsum and glabella in 1 case.¹⁵ Asymmetry due to impaired healing between nostrils (2 patients) and eyebrows (1 patient) was documented.^{15,16,43} Rare complication, such as temporary hearing loss, alopecia and atrophy of tongue, were reported as well.^{11,17,34}

Conversely, the majority of ophthalmic complications are usually catastrophic (see Tables 3 and 4). Out of 30 patients documented with these types of complications, 18 patients experienced complete unilateral loss of vision following injection. The injection areas found to be related to visual loss, as expected by the distribution of the ophthalmic artery branches out of the orbit, were mainly the nose

as well as the glabella and forehead. On 1 rare occasion, injection of HA to the midface resulted in complete vision loss. Complete resolution of symptoms was documented in 7 patients, among which, 6 patients initially presented with partial vision loss or blurry vision,^{4,48-50,57} and only in 1 case, a reverse of complete vision loss was achieved by the unique combination of fast intervention along with hyaluronidase “flooding” approach.⁴⁵ Where full recovery was achieved, in 5 cases the initial intervention was immediate,^{45,48,49,57} in 1 case the intervention took place 12 hours after injection⁵⁰ and in another case the timing of the initial intervention was not documented.⁴ Although not resulting in full recovery, 1 report of reversing complete vision loss to return of ability to follow hand movement was reported. The intervention in this case was administered 7 hours after the onset of symptoms. Eight patients in total had their vision loss successfully managed.⁴⁶ Hyaluronidase was used in 7 of these cases, but the amount varied between 60 and 2000 Units, and technique pattern was not repetitive. In 1 case, hyaluronidase was injected into the initial injection area, in others, injection was periorbital and retrobulbar, and in another case the technique was not specified.

Lastly, hyperbaric oxygen therapy was administered in 3 out of the previously mentioned 8 patients.^{46,57} Two other cases of partial recoveries of ophthalmic complications were also reported (except of the abovementioned), in 1 case hyaluronidase was administered in subcutaneous plane but timing and dosage were not specified and in another case no hyaluronidase was administered at all. A combination of steroids, antibiotics and vasodilators was given in 2 out of these 3 mentioned reports. Although complete resolution was not achieved, these reports should be emphasized as even slight improvement in visual acuity or extraocular movement can have a tremendous impact.^{47,52}

Limitations

This review did not include studies published in languages other than English so it is possible that some studies were missed. Studies included were retrospective with most having small sample size. As only case studies and series were found and included, the strength of evidence may be considered low. Other materials that are used as fillers were not included and might benefit from treatment as described for granulomas and abscesses. Whilst the algorithm presented is based on this review, extrapolating reliable data is limited, however our clinical experience has also informed the algorithm presented. Finally, many patients receiving HA fillers do so in private offices not affiliated with hospitals, therefore, the use of this proposed algorithm may not be universally applicable.

Conclusions

As popularity of injecting HA is increasing, and although safety measures are being taken to prevent complications

that can lead to tissue ischemia, these incidents may still occur. Vascular and ophthalmic complication will require a fast and effective intervention to reverse or at least prevent further damage. In this article, we reviewed all available literature related to these complications which provided appropriate information regarding the management and outcomes. We propose here a simplified, step-by-step algorithm for a straightforward approach in the ER for these situations, including filler injection-related abscesses approach.

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