Review

Complications of Periorbital Cosmetic Hyaluronic Acid Filler Injections: A Major Review

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Abstract

Hyaluronic acid (HA) filler injection is one of the most common methods for managing signs of aging in the periorbital area and is considered a safe and reversible procedure. The purpose of this review was to perform a comprehensive analysis of the incidence, risk factors, pathophysiology, signs and symptoms, and treatment methods of complications related to cosmetic periocular HA filler injections, as well as review hyaluronidase indications, appropriate dosage, and safety measures. Complications were classified as immediate injection-related reactions (erythema, early edema, bruising/hematoma), early complications (loss of vision, acute infection, early contour irregularities, persistent edema), late complications (late edema, late contour irregularities), blue discoloration, xanthelasma palpebrarum, and filler in the orbit. Prospective and retrospective studies as well as case reports were reviewed. Immediate injection-related reactions such as erythema, edema, and bruising/hematoma were the most reported complications, followed by early contour irregularities and blue discoloration. Persistent and late edema and late contour irregularities were reported less frequently. These were mainly minor complications that were reversible through conservative management or hyaluronidase injection. Filler-related loss of vision, xanthelasma palpebrarum, and filler in the orbit were infrequent but potentially serious complications that could cause patients significant distress. These were mainly reported through case reports and case series. Urgent treatment with high dose hyaluronidase is necessary for successful management of injection-related vision loss. Physicians must have a thorough knowledge of orbital anatomy, the signs and symptoms of complications, and how to avoid them, and must be equipped to intervene immediately if necessary.

Keywords: Hyaluronic acid, complication, edema, nodules, blue discoloration, inflammation, infection, vision loss

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Introduction

Facial aging is characterized by three main components: volume loss, gravitational tissue descent, and deterioration of skin quality and laxity. The most common signs of aging in the periorbital region are the formation of tear troughs, prominent upper eyelid sulcus, brow descent, and wrinkles. All of these contribute to a "tired" and "old" appearance that leads individuals to seek rejuvenating treatments.[1] Hyaluronic acid (HA) is a hydrophilic material that can increase skin turgor and hydration. It activates dermal fibroblasts, stimulates collagen neogenesis, and acts as an anti-inflammatory agent in certain forms.[2] Injected HA can be degraded using hyaluronidase, providing patients and physicians with a sense of reversibility and safety.[3] These properties make HA a near-ideal material, and injection of HA fillers is one of the most preferred rejuvenation methods.

There are various types of HA fillers with different rheologic properties, molecular weight, and crosslinking techniques, all produced for specific regions and indications.[2,4] The elastic modulus (G') of an HA filler represents its capacity to return to its original form once a shearing stress is removed. A filler with higher G' is firmer, more resistant to tissue pressure, more durable, and has more lift power. The viscous modulus (G'') represents the resistance to dynamic forces. A filler with higher G'' has less liquid-like properties and is less prone to deform and flow when injected into tissue.[5,6,7]

HA filler injection has been used in the periorbital area since the early 2000s and is generally regarded as a safe and effective method with high patient satisfaction.[8] However, several complications ranging from minor injection site reactions to chronic edema and contour irregularities, filler migration, and rarely, vision loss can be encountered. While some complications are related to injection technique or filler properties, the exact reason for others is yet to be understood.[3] With the increasing popularity of filler injection, an increase in the rate of these

adverse events is inevitable. The purpose of this paper was to report the frequency, findings, risk factors, and methods for prevention and treatment of complications related to cosmetic periorbital HA filler injections through a systematic review of retrospective and prospective studies and case reports. We also addressed hyaluronidase indications, appropriate dosage, and safety measures.

I. Immediate injection-related reactions: These are categorized as erythema, early edema, and bruising/hematoma.

Erythema

Erythema is reddening of the skin due to vasodilation triggered by a cutaneous inflammatory reaction to an irritant factor.[9] It is usually mild and transient, with the highest reported rate being 40% in one study. Rates of erythema in various studies are presented in Table 1.[10-36] Preexisting skin conditions like rosacea and certain injection techniques like serial needle injection are risk factors for erythema.[27,37] Waiting 1 month after the treatment of dermatitis and up to 3 months after the treatment of active rosacea is recommended to avoid inflammatory reactions.[3] Cold application, short-term steroid ointments, and vitamin K cream can be used to manage erythema.[37]

Early Edema

Early edema can occur as reaction to skin and soft tissue trauma caused by injection, or due to a type 1 hypersensitivity reaction (HSR).

Injection-related early edema has been reported at rates of 0-100% (Table 1).[10-36] Needle injection and lower viscosity HA gels were associated with lower rates of edema.[11,27,32] Avoiding frequent passes with needle, using ice packs before and after injection, and avoiding alcohol consumption for 12-24 hours before and after injection are beneficial measures.[14,38] Using antihistamines for patients with known previous allergic reactions, mixing filler with triamcinolone or silicate creams, and preferring an upright sleeping position are other recommended precautions against injection-related edema.[39]

Type 1 HSR (angioedema) should be kept in mind in cases of excessive bilateral generalized eyelid edema starting within minutes to hours after injection. Urticaria and itching may accompany. Medical treatment is via oral antihistaminics and corticosteroids. Patients should be monitored closely, as generalized symptoms involving the respiratory, gastrointestinal, or cardiovascular systems require hospitalization with intravenous treatment.[3,40]

Bruising/Hematoma

Bruising and hematomas occur due to compromised vascular integrity. This complication is rather common, with rates of 0-100% in various studies (Table 1).[10-36] Using a 22-gauge or thinner cannula is reported to result in lower rates of bruising compared to needles.[27,32] Marking the injection site beforehand, avoiding frequent passes with the needle, and applying ice before and after injections are other beneficial measures.[11] A cardiology consultation should be requested for patients on anticoagulants to weigh the risks and benefits of discontinuation. As certain supplements such as garlic, hawthorn, gingko biloba, chondroitin-glucosamine, echinacea, aloe vera, and St. John's wort are shown to increase the risk of bleeding, physicians must take a detailed history of dietary supplements and advise patients to avoid these ingredients for 2 weeks prior to injection.[41] Alcohol should be avoided for 12-24 hours before and after injection.[11,14,38] Bruising is usually mild and disappears within a few days with conservative interventions such as ice packing.

II. Early complications: These are categorized as vision loss, acute infection, persistent edema, and early contour irregularities.

Vision Loss

1. Filler Embolization of Vascular Structures

Although rare, partial or complete loss of vision resulting from arterial occlusion after HA injection is one of the most devastating complications of fillers. None of the studies in this review reported vision loss. However, according to a recent review of 60 documented cases of filler-related vision loss between 2015 and 2018, the injection area was the brow in 3 (5%) of the cases and the tear trough in 1 (1.7%).[42] Vision loss with or without pain usually occurs immediately, within minutes to hours, or up to a day in rare cases. Vision can range from no light perception to Snellen 0.7, depending on the scale of vascular involvement.[43] Nausea or vomiting, ophthalmoplegia, exotropia, ptosis, skin necrosis, and acute ischemic stroke may be among associated signs and symptoms.[42]

The supratrochlear artery (STA), supraorbital artery (SOA), dorsal nasal artery (DNA), and angular artery (AA) are distal branches of the ophthalmic artery (OA). Inadvertent injection into these arteries can lead to retrograde embolization of the OA, central retinal artery, and choroidal arteries, or may cause posterior ischemic optic neuropathy, leading to vision loss.[42,44] In the tear trough, the area between a line crossing the medial pupil and the lateral wall of the nose is described as a danger zone due to the presence of anastomoses of the nasal branch of the infraorbital artery to the STA, DNA, and AA.[45] Injection into the STA, SOA, and their branches is the main concern during superior sulcus and brow injections.[44]

Excellent knowledge of anatomy and compliance with injection guidelines are important to avoid arterial embolization. Using blunt cannulas or small-bore needles and smaller syringes, withdrawing before injection, gentle and slow injection with multiple small boluses, and avoiding previously traumatized areas are among the suggested precautions.[3,44] High frequency ultrasound is suggested as a potential tool to help avoid vascular complications during injection by simultaneously identifying injection planes and danger zones such as the infraorbital foramen.[46] Injection must stop as soon as the patient complains of pain or vision loss. Immediate injection of hyaluronidase is the main intervention technique. The hyaluronidase dose reported in studies varies between 500 and 3000 IU, and reported injection sites are subcutaneous, retrobulbar, the infraorbital foramen, the supratrochlear and supraorbital notches, and intraarterial to the OA.[42,47] Early injection and degree of initial vision loss are considered the most important factors for treatment

Table 1. Characteristics and complication rates of studies of cosmetic hyaluronic acid filler injection in the periorbital area

Study	Treatment area	Filler agent/ method	Patient number	Follow-up*	Erythema	Bruising	Early edema	Early contour irregularity	Blue discoloration	Persistent edema	Late edema	Vision loss	Late contour irregularity
Goldberg et al.[10], 2006	Infraorbital, eyebrow	Restylane/ suborbicularis	155	Up to 12 mo	0 (0%)	42 (27%)	18 (15%)	18 (15%)	12 (10%)	5 (3%)	0 (0%)	0 (0%)	0 (0%)
Morley et al.[11], 2009	Eyebrow	Restylane/ preperiosteal	27	Mean 13 mo	0 (0%)	27 (100%)	27 (100%)	0 (0%)	N/A	0 (0%)	1 (3.7%)	0 (0%)	0 (0%)
Berros[53], 2010	Infraorbital	Restylane/ preperiosteal	26	3 mo	0 (0%)	7 (13%)	12 (21%)	2 (14%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Choi et al.[13], 2011	Upper eyelid/ superior sulcus	Restylane/ suborbicularis	7	Mean 9.6 (3-18) mo	0 (0%)	7 (100%)	7 (100%)	0 (0%)	N/A	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Morley and Malhotra[14], 2011	Infraorbital	Perlane/ suborbicularis	100	Mean 5.1 (1-18) mo	0 (0%)	75 (75%)	26 (26%)	33 (33%)	4 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Viana et al.[15], 2011	Infraorbital	Restylane/ preperiosteal	25	Mean 9.5 (8-15) mo	10 (40%)	13 (52%)	2 (8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
De Pasquale et al.[16], 2012	Infraorbital	Uma Jeunesse/ suborbicularis	22	36 mo	0 (0%)	4 (18.2%)	2 (9.1%)	6 (27.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Berguiga and Galatoire[17], 2017	Infraorbital	Teosyal Puresense Redensity II/ suborbicularis	151	Up to 1 mo	7 (6%)	17 (11.3%)	22 (14.6%)	0 (0%)	4 (2.6%)	1 (0.9%)	N/A	0 (0%)	0 (0%)
Niforos et al.[18], 2017	Infraorbital	Juvederm Volbella-L/deep plane	80	Up to 12 mo	38%	39%	26%	33%	3 (4%)	0 (0%)	4 (5%)	0 (0%)	0 (0%)
Mustak et al.[19], 2018	Infraorbital, eyebrow	Restylane/ suborbicularis	147	Mean 6.3 (5-9) y	Not specified	Not specified	Not specified	Not specified	46 (31.3%)	17 (11.5%)	Not specified	0 (0%)	45 (30.5%)
Cho et al.[20], 2018	Infraorbital	Cleviel Fine/*not specified*	9	24 wk	0 (0%)	1 (11%)	6 (66%)	0 (0%)	0 (0%)	0 (0%)	N/A	0 (0%)	0 (0%)
Hall et al.[21], 2018	Infraorbital	Juvederm Voluma XC/suborbicularis	101	Mean 12 (4-17) mo	0 (0%)	10 (10%)	3 (3%)	2 (2%)	1 (1%)	3 (3%)	0 (0%)	0 (0%)	0 (0%)
Hussain et al.[22], 2018	Infraorbital	Juvederm Ultraplus XC/ suborbicularis	150	12 mo	6 (4%)	3 (2%)	12 (8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Mustak et al.[23], 2018	Eyebrow	Restylane-L/ ROOF	20	At least 5 y	0 (0%)	0 (0%)	0 (0%)	0 (0%)	N/A	3 (15%)	0 (0%)	0 (0%)	0 (0%)
Romeo[24], 2019	Eyebrow	Yvoire volume+/ ROOF	427	At least 12 mo	0 (0%)	0 (0%)	2 (0.4%)	0 (0%)	N/A	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Diwan et al.[25], 2020	Infraorbital	Teosyal Puresense Redensity II/ preperiosteal	24	4 wk	0 (0%)	1 (4.1%)	4 (16.6%)	0 (0%)	0 (0%)	0 (0%)	N/A	0 (0%)	N/A

Table 1. Continued

Study	Treatment area	Filler agent/ method	Patient number	Follow-up*	Erythema	Bruising	Early edema	Early contour irregularity	Blue discoloration	Persistent edema	Late edema	Vision loss	Late contour irregularity
Fabi et al.[26], 2021	Infraorbital	Juvederm Volbella-L/ suborbicularis	103	12 mo	0 (0%)	4 (3.8%)	3 (2.9%)	0 (0%)	6 (5.8%)	0 (0%)	3 (2.9%)	0 (0%)	0 (0%)
Nanda et al.[27], 2021	Infraorbital	Crosslinked HA/ suborbicularis	60	12 mo	20 (33%)	5 (8.3%)	5 (8.3%)	4 (6.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Scarano et al.[28], 2021	Eyebrow	Crosslinked HA/ ROOF	15	6 mo	0 (0%)	0 (0%)	0 (0%)	0 (0%)	N/A	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Shah-Desai and Joganathan[29], 2021	Infraorbital	Restylane Vital Light/subdermal	165	Mdn 6 (6-36) mo	0 (0%)	100 (60.6%)	2 (1.2%)	0 (0%)	3 (1.8%)	2 (1.2%)	0 (0%)	0 (0%)	0 (0%)
Vadera et al.[30], 2021	Infraorbital	Juvederm Volbella/ subdermal	15	24 mo	0 (0%)	4 (26.6%)	0 (0%)	0 (0%)	2 (13.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Juvederm Voluma/ supraperiosteal	15	24 mo	0 (0%)	1 (6.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Wollina and Goldman[31], 2021	Infraorbital	Belotero supraperiosteal	45	-	0 (0%)	4 (8,8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Diaspro et al.[32], 2022	Infraorbital	Teosyal PureSense Redensity II/ suborbicularis	600	Mean 12 (4-17) mo	14 (2.3%)	6 (1%)	16 (2.6%)	0 (0%)	27 (4.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Lee et al.[33], 2022	Infraorbital, crow's feet	Yvoire-Hydro/ intradermal	27	28 wk	1 (3.7%)	0 (0%)	0 (0%)	1 (3.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Can and BetülGözel[34], 2022	Upper eyelid	Low-viscosity HA/ supraperiosteal	25	Mdn 14 mo	0(0%)	0 (0%)	25 (100%)	0 (0%)	-	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Biesman et al.[35], 2024	Infraorbital	Resytlane Eyelight/ supraperiosteal	287	12 mo	0 (0%)	5 (1.6%)	12 (3.8%)	4 (1.3%)	1 (0.3%)	4 (1.3%)	0 (0%)	0 (0%)	0 (0%)
Fakih-Gomez et al.[36], 2024	Infraorbital	CPM-B/ retroseptal/ supraperiosteal	198	-	0 (0%)	1 (0.5%)	1 (0.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

*Follow-up times given in weeks (wk), months (mo), or years (y), with mean or median (med) and range in parentheses when available. HA: Hyaluronic acid, ROOF: Retro-orbicularis oculi fat, N/A: Not applicable

success. Still, 50% success within minutes was reported for hyaluronidase injection. Ocular massage, hyperbaric oxygen, intravenous steroid or mannitol, acetazolamide, and antiplatelet agents are among the various documented interventions.[3,40,42,44]

2. Globe Perforation

Inadvertent globe perforation and intraocular filler injection is another rare cause of filler-related vision loss, with two reported cases in the literature. One study reported a case where filler was injected into the anterior chamber via a lamellar corneal perforation,[48] and another reported intravitreal HA injection accompanied by retinal hole and small localized vitreous hemorrhage.[49] In both patients, symptoms included dull pain, chemosis, and blurred vision. No intraocular infection or significant inflammation was seen in either case. In the first case, HA was removed via irrigation and aspiration, leading to complete recovery.[48] In the latter case, the retinal hole was treated with laser photocoagulation and the HA was left in the vitreous under close observation, with no further complications other than cloudy vision at 2-months follow-up.[49]

To avoid this problem, all injections must be performed by licensed and well-trained practitioners. Conformers may be used to protect the cornea when injection is performed by inexperienced physicians or during cases with risk factors such as degenerative myopia or thyroid eye disease. Physicians must be able to recognize the signs and symptoms and be prepared to either intervene immediately, or refer the patient to an adequate ophthalmological center urgently.[48]

Acute Infection

Infection/cellulitis of the eyelid skin is rare. The reported incidence is 0.04% to 0.7%.[50,51] Acute infection presents as persistent edema accompanied by erythema, fluctuance, pain, and occasionally nodules.[52] The most common causative agents are Staphylococcus aureus and Streptococcus pyogenes. However, atypical bacteria should be suspected in cases occurring later than 2 weeks after injection.[40] Staphylococcal cellulitis may be accompanied by abscess formation.[50] Physicians should comply with the rules of sterile injection, and patients should be properly informed about postinterventional care to minimize the risk.[3] Amoxicillin-clavulanate or clindamycin are recommended empiric antibiotics for first-line treatment. Topical antibiotics can be utilized in conjunction with systemic therapy. Abscesses should be drained and cultured to test antibiotic sensitivity. Patients should be monitored for systemic findings and admitted to hospital if necessary.[40]

Herpes simplex reactivation is another complication that physicians must be aware of, although this occurs more commonly after lip injections. Patients present with typical herpetic vesicles and lymphadenopathy. Systemic antiviral therapy should be started promptly in such cases.[40]

Acute conjunctivitis was reported in one patient of a series that included 24 upper eyelid injections. In this case, conjunctivitis was caused by inadvertent injection of filler into the bulbar conjunctiva and was treated by surgical removal.[50]

Early Contour Irregularities

Early contour irregularities occur due to clumps of non-homogenously dispersed fillers and can be seen in up to 33% of patients (Table 1).[10-36] Thin eyelid skin and lack of subcutaneous fat tissue in the infraorbital region contribute to the aesthetically displeasing nature of this complication. Overcorrection, superficial placement,[40] and fillers with higher G' and G" values are reported risk factors.[10,14,53] Deep preperiosteal injections, using fillers with lower G' and G" values,[5] and massaging afterwards are the main methods of minimizing irregularities while maintaining sufficient volume restoration. Shah-Desai and Joganathan[29] reported subdermal microdroplet injection of very low G' and G" materials with a 0% rate of contour irregularities and proposed this method for infraorbital injection in younger patients who require less volume restoration.

When encountered, treatment options include massage and additional HA injections to smoothen the appearance of the area. Dissolving the filler with hyaluronidase is effective for cases that do not respond to conservative management.[40] Dosage varies according to the filler material and extent of nodules, and doses of 5 to 150 units have been reported.[54]

Persistent Edema

Persistent edema starts within days after injection and persists for more than 4 weeks despite conservative management.[23,55,56] Its prevalence varies between 0% and 15% (Table 1).[10-36] It is non-inflammatory and non-erythematous, with a soft, pale appearance that may resemble fluid sacs. In the infraorbital area it extends beyond the borders of the injection site through the malar eminence, which is often referred to as malar edema.[10] On the upper eyelids it can present as puffiness around the eyes or pale edema of the upper eyelids and brow area without inflammatory findings.[23,55]

In the infraorbital region, edema is thought to occur due to accumulation of filler and extracellular fluid superficial to the malar septum. The malar septum is a fibrous barrier that starts at the level of the inferior orbital rim and inserts into the cheek skin approximately 3 mm below the lateral canthus, at the level of the inferior border of the orbicularis oculi muscle. It divides the suborbicularis oculi fat into superior and inferior compartments. Its relative impermeability leads to accumulation of edema within the superiorly located structures. Injection superficial to this landmark may cause edematous accumulation, exacerbated by compression of periorbital lymphatic flow by the filler material. Hydrophilic fillers with high water uptake, such as those crosslinked with Hyalocross technology, can also lead to higher rates of persistent edema.[5,39,52]

Older age, skin laxity, associated skin problems (allergies, rosacea), preexisting malar mounds, and herniated fat pads are patient-related risk factors.[3,10]

Obtaining a detailed patient history and careful physical examination and patient selection are important steps to avoid persistent edema. Performing consecutive injections less frequently, using lower volumes, and opting for deep preperiosteal

injections can decrease the risk of persistent edema.[17,56] However, the level of the initial injection may not always correspond to the final localization of the filler, as anterior migration can occur based on anatomical variances and filler properties.[57]

Upon encountering persistent edema, physicians should look for any accompanying sign of inflammation such as redness, tenderness, and nodules to rule out infection or delayed inflammatory reactions.[40]

Close follow-up with ice packing, elevating the head at night, and periorbital massage to increase lymphatic drainage may be effective for treatment.[29,40] Topical treatment includes cortisone creams, silicate creams, and triamcinolone injections.[39] Hyaluronidase injection of 10-50 units is usually effective in cases not responsive to conservative treatment.[10,51,56] Nevertheless, some cases may not completely resolve with hyaluronidase, and cases requiring up to 750 units over multiple sessions are reported in the literature.[10,39,52]

III. Late complications: These are categorized as late edema and late contour irregularities.

Late Edema

Late edema appears 1 month to years after injection.[11,58,59,60] Although the exact prevalence is unknown, studies show that it may occur in up to 5% of cases before the end of 12-month follow-up.[11,18] It can affect both the upper and lower eyelids. In a study of 78 patients with late periorbital edema, 17 cases involved upper eyelids while 61 involved lower eyelids.[61] Late edema of the upper eyelids may present as superomedial edema, centrolateral brow edema, or upper lid edema with ptosis.[61] In the lower eyelids, it presents as late chronic edema that may be accompanied by the Tyndall effect and may worsen over time.[62] There is no accompanying signs of inflammation such as redness, tenderness, or nodules.[19,59,63]

The underlying mechanism is a subject of debate. Dubinsky-Pertzov et al.[61] and Skippen et al.[62] proposed that the main mechanism was HA incarceration within the orbicularis oculi fibers leading to muscle degeneration. Histologic studies show that HA in the human body is not always completely degraded by natural processes, and some material can remain within tissues even several years after injection. This leads to degeneration of the orbicularis oculi fibers, which are then surrounded by pools of excess extracellular matrix.[60] Furthermore, they argued that HA is a hydrophilic material that undergoes isovolumetric degradation in which each particle interacts with water as the filler breaks down, thus preserving the total volume. This process, along with a reduction in orbicularis oculi contractional function which would normally aid in lymphatic fluid flow, may lead to edema even years after injection.[61,62] More hydrophilic materials such as Hyalocross and Vycross family fillers may be more prone to cause late edema.[52]

When encountering a case of periocular edema, it is important to be highly suspicious of and persistently question for a history of fillers. Patients may be reluctant to admit to or forget getting filler injections.[52] Late non-inflammatory periorbital edema should be differentiated from delayed HSR, where edema is associated with induration, nodules, and other inflammatory findings.[64]

Hyaluronidase is reported to be sufficient for resolution of late edema even in cases that last several years. Dosage depends on the extend of edema and varies between 30 and 90 units.[61,62]

Late Contour Irregularities

Late contour irregularities may present as palpable masses or nodules, with or without accompanying edema and inflammation, weeks to months after injection.[3] The incidence is unclear because most studies had short-term follow-up, and our knowledge about this complication is mainly from case reports or series. Mustak et al.[19] reported a frequency of 30.5% in their series of patients with at least 5-year follow-up, with most cases being mild irregularities not requiring intervention. Late irregularities may be attributed to non-inflammatory mechanisms such as filler capsule contraction[65] or to delayed inflammatory reactions that include foreign body granuloma, biofilms, atypical infectious granuloma, and delayed type 4 HSR.[64]

Non-inflammatory late nodules are infrequent. They present as firm masses with clear borders and no inflammatory findings. Microscopic examination shows encapsulated Alcian blue-staining HA with no surrounding inflammatory cells. They are usually resolved by surgical excision of the mass.[65,66]

Inflammatory nodules are accompanied by erythematous edema and tenderness.[67,68,69] The exact etiology may be difficult to identify with only clinical findings and skin sensitivity tests, and histopathological examination of biopsy material, tissue cultures, and polymerase chain reaction tests may be required for definitive diagnosis.[4,64] In a histopathological study of nodules after various types of filler injections, granuloma due to foreign body reaction and atypical infectious granuloma were reported as the most common etiologies.[70]

Foreign body granuloma occurs due to chronic activation of macrophages and lymphocytes around a foreign object that cannot be removed via enzymatic degradation or phagocytosis.[64,70] Histopathology reveals histiocytes and multinucleated giant cells surrounded by lymphocytes and eosinophiles.[67,68] Crosslinked filler agents are more resistant to enzymatic degradation and may be more prone to cause foreign body granulomas,[4] although there is no definitive conclusion in the literature due to data scarcity and lack of a detailed filler history in these cases. Immune system reactivity or previous viral infections may also play a role.[4,40]

Biofilms are caused by contamination of filler with skin microbiota such as *S. aureus* and *Cutibacterium acnes*. A biofilm consists of microbial cells and an extracellular polymeric substance. In time, biofilms may trigger a continuous immune response and lead to granulomatous inflammation and late nodules.[3,4,40]

Atypical infectious granuloma presents as suppurative or caseating granuloma with central caseation necrosis and prominent neutrophilic infiltrate on microscopy. Mycobacterial infection with *Mycobacterium fortuitum* and *Mycobacterium marinum* has been reported as the main cause.[70] Infection can also be caused by a combination of various microbiologic

agents such as fungal infection combined with *Escherichia coli*, *Enterococcus faecalis*, and *Staphylococcus epidermidis*, or various inflammatory mechanisms may be present at the same time.[69]

Delayed type 4 HSR is a cellular immune response to filler. Its general incidence after HA injections of all body parts is estimated to be 0.06%.[64] Although the immunogenicity of HA fillers is very low, HSR can still be triggered by many factors including molecular weight, additives, and the technology of HA production. Low-molecular-weight fillers are known to have proinflammatory properties. Crosslinking may also increase the immunogenicity of a filler by altering the natural configuration of HA.[4] Vycross family fillers are associated with higher rates of late-onset inflammatory nodules compared to other materials.[71]

Avoiding uncertified filler materials and complying with the rules of sterile injection are important steps to avoid atypical infections and biofilm formation.[40] Skin testing 3-4 weeks prior to injection can rule out any sensitivity to agents that could cause delayed HSR. If skin testing reveals sensitivity to a certain ingredient, a different material should be preferred.[64] Medical treatment and degradation of the filler with hyaluronidase is the main treatment. There is no uniform algorithm for the dosage of hyaluronidase, and doses ranging from 30 to 300 units in total to 500 units every 48 hours have been reported.[54] In cases of granulomatous inflammation, oral antibiotics should be added to reduce the risk of spreading the biofilm and infection. Lincosamides, macrolides, and tetracyclines are among the suggested antibiotic agents. The presence of type 4 HSR warrants the use of oral or intralesional corticosteroids. Some authors suggest using a combination of antibiotics and corticosteroids because it is difficult to differentiate infectious etiology from HSR in most cases.[3,4,40]

IV. Blue Discoloration (Tyndall Effect)

Blue discoloration is a well-known phenomenon that occurs after infraorbital HA injections. It can be observed weeks, months, or years after injection.[52] Its incidence varies between 0% and 31%, and higher rates are reported in studies with longer follow-up (Table 1).[10-37] It is often referred to as the Tyndall effect, a phenomenon that occurs due to dispersion of light from superficially located filler under the thin and translucent lower eyelid skin.[72] However, some authors challenge this term and suggest that the light is not scattered by the filler itself, but by colloidal material within superficial edema, especially in cases where blue discoloration occurs months to years after injection.[39,73]

Many factors are related to blue discoloration, including injection location, use of needle vs. cannula, rheological properties, and crosslinking technology.

Injecting into the suborbicular or supraperiosteal plane leads to lower rates of blue discoloration.[17,26] Diaspro et al.[32] stated that needle injection is superior to cannula because it allows placement of single bolus of filler into the desired deeper location, whereas a cannula is more prone to result in superior misplacement. If the physician opts for a cannula, injecting multiple small boluses and firmly massaging the area are recommended.

The G' and G'' values of the filler may also play a role in the development of blue discoloration. Fillers with lower G' and G'' values are reported to be less likely to cause blue discoloration despite more superior injections.[74] However, Vadera et al.[30] conducted a study where they compared a lower G' filler injected subdermally at the medial, central, and lateral infraorbital area to a higher G' filler injected in the deep supraperiosteal plane at the lateral and inferolateral periorbital rim. They concluded that the latter technique led to a dramatic decrease in blue discoloration, required less filler volume, and had a longer-lasting effect.

On the other hand, recent studies using fillers with very low G' and G'' values, marketed as "skin boosters", or fillers that contain non-crosslinked HA suggest that these products can be applied subdermally or intradermally with blue discoloration rates as low as 0-1.8%. Still, it must be kept in mind that these products have less volume-enhancing qualities and mainly target superficial wrinkles.[29,33]

Crosslinking technology may also play a role in blue discoloration. It is recommended to refrain from injecting Hyalocross fillers superficially despite their lower G' and G'' because they are more hydrophilic and tend to bind more water and may cause more prominent blue discoloration.[39,52] However, Hussain et al.[22] reported no blue discoloration with a filler from the Hyalocross family. Vycross family fillers were also noted to cause blue discoloration more frequently.[52]

Hyaluronidase injection is usually sufficient for treatment. The required dose may vary according to filler material and volume, and doses of 30-75 units have been reported.[75]

V. Xanthelasma Palpebrarum

Xanthelasma or xanthelasma-like lesions on the eyelids after HA filler injection are rare, with only six reported incidences in the literature.[76,77,78,79] All the cases were located on the lower eyelids and appeared as yellowish plaques around the injected area a few weeks to months after injection. Examination usually reveals no significant hyperlipidemia. Histopathological examinations reveal foamy histiocytes filled with lipid droplets, macrophages containing material suggestive of HA fragments, and extracellular lipids in the superficial dermis.[76,77] Although the exact mechanism is not known, binding of filler with extravasated low-density lipoprotein in tissues leading to phagocytosis by macrophages is considered a possible mechanism.[76] Hyaluronidase injection, steroid injection, fluorouracil (5-FU) injection, ablative or fractionated carbon dioxide laser, erbium-doped yttrium aluminum garnet laser ablation, or surgical excision are reported as plausible treatment approaches.[76,77,78,79]

VI. Filler in the Orbit

Filler in the orbit is a rare complication that can occur due to inadvertent penetration of the orbital septum during injection,[80,81,82] or migration of filler material into the orbit.[83]

Inadvertent penetration of the septum may result in filler placement within the orbital fat pad or around the extraocular muscles. This can cause further bulging of the orbital fat pad and worsen the patient's appearance,[81] cause myositis of the

periocular muscles,[80] or lead to sight-threatening retrobulbar hemorrhage if orbital vessels are perforated.[82] Herniated fat pads, orbital rim thinning, and orbital septum weakening are among the risk factors for inadvertent septal perforation. Although preperiosteal needle injection is associated with higher risk, cannula injections can also lead to filler placement within the orbital fat pad.[81] Surgical removal or degradation with hyaluronidase are treatment methods. Lateral canthotomy and cantholysis is required if orbital compartment syndrome occurs.[82]

Migration of filler into the orbit can occur after filler injection to the periorbital area or various facial areas such as the glabella, temples, zygoma, midface, or nasolabial folds.[84] The most common symptoms are periorbital edema and a palpable mass that may appear months or years after injection. Inflammation and fibrosis within the orbit can lead to palsy of the intraorbital nerves, such as partial third nerve palsy leading to adduction deficiency.[84] The inferior oblique muscle is located near the orbital fat and capsulopalpebral fascia. Filler materials migrating around it can cause delayed HSR or foreign body reaction and subsequent inflammation of the muscle, leading to vertical diplopia.[80] Migration into the nasolacrimal sac can cause nasolacrimal obstruction.[84] Forceful injection of high amounts of filler and vigorous massaging are among the proposed causes of filler migration.[85]

Diagnosis based on clinical history alone may not be possible in many cases. Orbital imaging via computed tomography or magnetic resonance imaging is useful to determine the location of filler or filler-related inflammation. Orbitotomy and histopathological examination is performed for definitive diagnosis.[84] Treatment is via surgical excision of the filler, degradation using hyaluronidase, or a combination of both.[84] Intraorbital injection of up to 120 IU hyaluronidase is reported to be safe and effective.

Mechanisms and Safety of Hyaluronidase for the Treatment of Hyaluronic Acid Filler-related Complications

Hyaluronidase is the main agent in the treatment of many HA filler complications. The required dosage varies depending on injection site, filler type, and amount of filler. Fillers with higher HA concentration and greater degree of crosslinking require higher doses of hyaluronidase.[86]

Although hyaluronidase administration is generally regarded as a safe procedure, physicians should be aware of potential HSRs such as local cutaneous reactions (0.05-0.69%), urticaria and angioedema (<0.1%), and anaphylaxis, which is rare. An intradermal sensitivity test is recommended prior to elective injections. Concomitant use of nonsteroidal anti-inflammatory drugs, aspirin, and vitamin C may decrease the efficacy of hyaluronidase.[3,40]

Conclusion

In this paper, we provided a detailed review of the literature on complications of cosmetic periorbital HA filler injections. The reviewed papers present heterogeneous information, as the authors used different fillers and described various injection techniques and locations. Furthermore, heterogenous terminology was used to describe similar complications. Some studies had small cohorts and short follow-up times that may not accurately reflect the incidence of long-term complications. Less common complications that develop months to years after injection were reported only in case reports.

Most complications associated with periorbital HA filler injection are mild-to-moderate immediate injection-related complications that are usually managed with conservative methods. Early contour irregularities, persistent edema, and blue discoloration are less frequent. Careful patient selection, avoiding highly hydrophilic materials, and injecting in the preperiosteal plane are important precautions. Hyaluronidase is usually effective as treatment. Acute infection is infrequent in the periorbital region, and late-onset atypical infections usually present as late-onset nodules. Knowledge is limited regarding the incidence and pathomechanisms of certain complications such as xanthelasma palpebrarum, late-onset edema, late contour irregularities, and filler in the orbit. Future studies with longer follow-up are necessary to acquire more information about these complications. Filler-related vision loss is a rare but devastating complication which is usually preventable by avoiding danger zones and injecting meticulously. Early diagnosis and prompt intervention are the most important factors for recovery.

Physicians should be thoroughly trained on the anatomy of the periocular area, the rheological properties of fillers and correct injection methods, the warning signs and symptoms of possible serious complications, methods for avoiding complications, and proper management techniques.

Declarations

Authorship Contributions

Concept: M.B.H., H.N.B., Design: M.B.H., H.N.B., Data Collection or Processing: H.N.B., Analysis or Interpretation: H.N.B., M.B.H., Literature Search: H.N.B., Writing: H.N.B., M.B.H.

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