Complications of Injectables

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KEYWORDS

• Neuromodulator • Eyelid ptosis • Brow ptosis • Dermal filler • Hyaluronic acid • Hyaluronidase • Vascular injection • Skin necrosis

KEY POINTS

- Understand pertinent facial anatomy prior to the administration of neuromodulators and dermal fillers.
- It is important to undertreat as more can always be added at subsequent follow up appointment.
- Be able to recognize early signs and symptoms of vascular occlusion of dermal fillers.
- Understand the recommended standard dosage of hyaluronidase for addressing vascular occlusion and determining treatment endpoints.

Introduction

In recent years, the demand for non-surgical esthetic procedures has been steadily rising. According to Aesthetic Surgery Report (2022), this category accounts for 28% of the total revenue of $11.8 billion.[1] Neuromodulators, skin treatments, and dermal fillers yield almost 80% of the revenue. They are the preferred choice for individuals seeking to rejuvenate their appearance, reduce signs of aging, and enhance their confidence. What sets neuromodulators and dermal fillers apart from their surgical counterpart is their ability to deliver remarkable results with minimal downtime. Nevertheless, it is important to recognize that even though minimally invasive techniques have brought significant changes to cosmetic medicine and surgery, they are not without their complexities and potential complications.

Complications of neuromodulators

There are currently 5 Food and Drug Administration-approved neuromodulators for facial rejuvenation in the United States. These include Botox (onabotulinumtoxinA), Dysport (abobotulinumtoxinA), Xeomin (incobotulinumtoxinA), Jeuveau (botulinum toxin type A), and Daxxify (daxibotulinumtoxinA-lanm) which basically are all injectables involving botulinum toxin. The difference is in their formulations.

Neuromodulators work by blocking the presynaptic release of the neurotransmitter acetylcholine at the neuromuscular junction, thereby inducing partial paralysis and atrophy of the muscle fibers. Based on this mechanism of action, selective delivery of the toxin to specific facial muscles could help soften fine lines and wrinkles. Therefore, it is imperative for the injector to fully understand the intricacies of facial anatomy and the required dosage to optimize treatments and to avoid unwanted complications.

Incidence of complications

Based on a review of 9398 botulinum toxin treatments, the most common adverse events are headache (5.38%) followed by nasopharyngitis (3.08%), and hypersensitivity reaction (2.90%).[2]

Headache/pain at injection site

Headache could be explained by the injected location of the procedure itself, with underlying cause of periosteal or intramuscular irritation, hematoma, and muscle spasm. The duration of such episode is short and temporary.

Hypersensitivity reactions

Allergic and hypersensitivity reactions although uncommon, have been reported. Transient localized cutaneous reactions, such as diffuse acneiform eruption of the forehead, are reported. Incidents of severe systemic allergy with generalized itching to anaphylaxis are rare.[3,4] Regardless of the severity of the reactions, the type of the hypersensitivity reactions needs to be examined to determine whether it is a type I or type IV, or pseudo-allergy reactions. Remember to rule out whether the disinfectants used could be a culprit in causing the event.

Local injection reactions

Edema, bruising, pain, ecchymosis, and discomfort only account for less than 1% based on the systematic review.[2] In our practice, the incidence of bruising is almost non-existence with the employment of 32-gauge needles, superficial injections, and direct avoidance of visible vessels under the surface of the skin. To further minimize the risk of bruising and patient discomfort, the needle is changed frequently. Patients remain in the office after injection with an ice pack in place for 5 to 10 minutes after their procedure.

Undertreatment and overtreatment

When patients seek neuromodulators for facial wrinkles, it is crucial to assess their treatment history, including prior neurotoxin injections, treated areas, dosages, and satisfaction. For Botox-naïve individuals, conservative treatment is often recommended, with results visible within 24 hours but

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optimal outcomes appearing up to 2 weeks post-injection. Follow-up visits ensure patients are satisfied even if touch-ups are not necessary.

Although a minority, some patients request the "frozen" look. It can be a challenge to find this balance to avoid over-treating the region. It is important to recognize that some patients are 'frontalis dependent.' They unconsciously hyper-animate and elevate their brows in order to alleviate brow ptosis or excessive upper eyelid dermatochalasis. In such patients, complete paralysis of the frontalis can appear to worsen this condition as patients can no longer activate the lower portion of the frontalis to lift the brows, which in turn lift the eyelids. They tend to complain that their brows feel heavy, "sleepy", and appear tired.

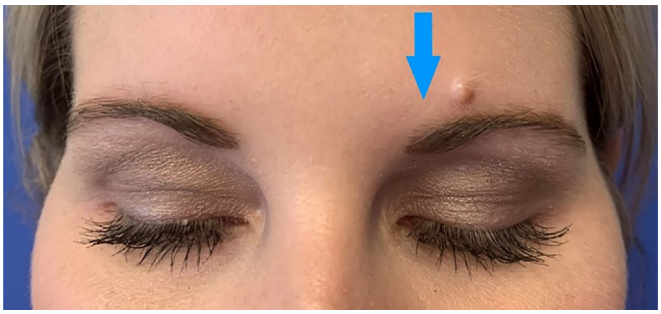

Fig. 2 Left brow ptosis after Botox treatment. Note the medial and middle portions of the left compared to the right brow.

Brow and eyelid ptosis

Ptosis could be iatrogenic and due to over injection of neuromodulators, trauma, aging, and developmental or genetic abnormalities. In the aging population, droopy brows, and eyelids are often observed. Surgical options are available to address these concerns such as brow lift and blepharoplasty. However, some patients do not want the down time and seek non-surgical options.

It is important to conceptualize that neuromodulators may be used to selectively weaken the antagonizing elevators and depressor of the brow. By weakening the depressors of the brow such as the corrugator, depressor supercilii, and the lateral portion of the orbicularis oculi, the brows can moderately be lifted with neurotoxin application. This is a result of altering the balance of the antagonistic musculature of the brow. On average, patients receive the recommended dosage in the glabellar region of 20 to 24 units in women and 24 to 32 units in men, 2 to 4 units in the lateral-superior portion of the orbicularis oculi, and 4 to 12 units in the lateral portion of the orbicularis oculi, 1 cm lateral from the lateral orbital rim as shown in Fig. 1. However, if the injector is not aware of the anatomic landmarks, ptosis of both the brow and eyelid can occur as shown in Figs. 2 and 3, leading to visual field disturbance.

Managements of brow and eyelid ptosis are often challenging as there are no effective and immediate reversal agents for neuromodulators. It is of paramount importance to prevent these complications from occurring with proper dosing and placement of neurotoxin.

Eyelid ptosis occurs when the injected neurotoxin diffuses through the orbital septum and reaches the levator palpebrae superioris, the elevator the upper lid. There are key anatomic landmarks to in this region. When injecting the lateral corrugator muscle, stay medial to the mid-pupillary line and be superficial, just right under the skin, as shown in Fig. 1. If the depth passes through the orbicularis oculi, there is potential for the toxin to pass through the orbital septum into the posterior lamellae, potentially leading to blepharoptosis.

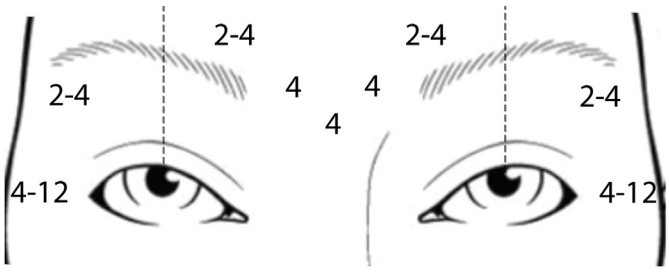

Fig. 1 Illustrative diagram for the typical dosage of Botox for the treatment of brow ptosis. Note that these dosages are starting point.

Blepharoptosis can also be explained by variations in the exit path of the supraorbital pedicles. One is through the supraorbital foramen and the other is through the supraorbital notch. For individuals with a more superior supraorbital foramen, this can be a shorter pathway for the toxin to spread into the orbit as shown in Fig. 4.[5] This can be alleviated by placing the thumb over the supraorbital notch and the injection needle pointing in the superior and lateral direction.

Some authors suggest diluting Botox with 1 mL of normal saline per 100 units yields a more concentrated neurotoxin solution that reduces the risk of toxin diffusion. The lesser volume afforded by this more concentrated dilution can help prevent unwanted diffusion through the supraorbital foramen/notch or into the levator palpebrae superioris if the depth of the injection is too deep. Nevertheless, the injectors need to be extremely precise in delivering the botulinum toxin to have the desired outcome. As a result of this, it is more common to dilute 100 units of Botox with 2.5 cc of normal saline to achieve a balance between precision and diffusion.

Treatment of eyelid ptosis

Several medical management options are available. The ophthalmic drops include oxymetazoline HCl 0.1% (Upneeq), apraclonidine 0.5% (Iopidine), and naphazoline and pheniramine (Naphcon A, available over-the-counter). They are adrenergic agonist agents that targets both alpha-1 and alpha-2 receptors. In addition to the levator palpebrae superioris muscle, which is the main upper lid elevator, Müller's muscle also assists in upper lid elevation. It is comprised of smooth muscle fibers of the sympathetic nervous system. By activating the adrenergic receptors of the Müller's muscle, eyelid ptosis can be ameliorated.

Brimonidine gel 0.33%, an adrenergic agonist, can also be used if patients cannot tolerate ophthalmic drops. It is applied over the skin of the upper eyelid and seems to have much lower side effects profile than the alternatives. Its effect however tends to be short-lived.[6,7]

Anticholinesterases are also an option if patients have a history of local allergy with alpha adrenergic ophthalmic drops. Improvement can be seen within 30 minutes at a 60 mg per os dose of pyridostigmine, effect lasts about 6 to 8 hours.[8]

Transdermal botulinum toxin injection in the pretarsal region to target the orbicularis oculi is another alternative.[9,10] Approximately 2 to 3 units 2 mm above the lash line. Improvement in minimal residual disease is observed between the 6 to 12 weeks mark. This method is technique sensitive. Thus, it is

Fig. 3 53-year-old female presented for treatment of left eyelid ptosis. She received the recommended dosage of Botox of 20 units for the glabella region, and 8 units each at 1 cm lateral to the lateral canthus and 2 units each at the tail of the brows. On the right, patient followed up 2 weeks after with sign of blepharoptosis of the left eye.

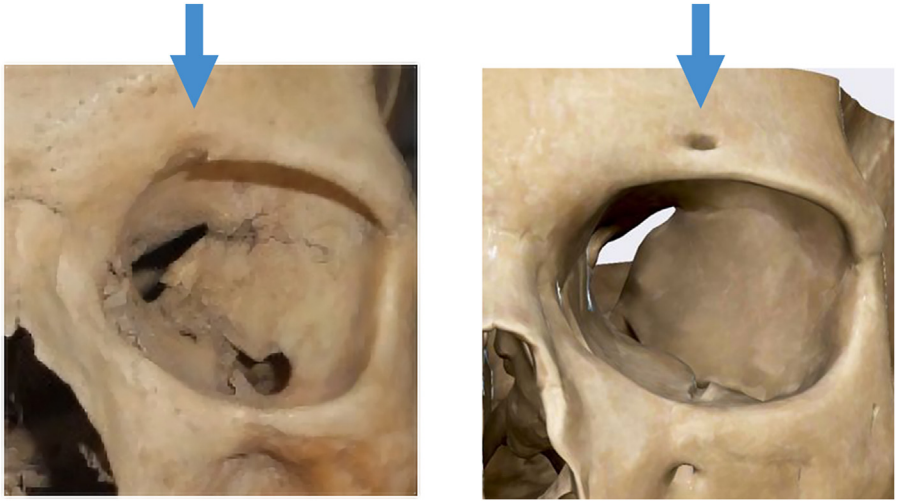

Fig. 4 Comparison between the supraorbital notch (left) and the supraorbital foramen (right). Their locations can serve as retrograde pathway for diffusion of toxin, especially the superiorly placed foramen.

Table 1 Treatment of Eyelid Ptosis, this table lists the currently available medical management of acquired blepharoptosis

Treatment of eyelid ptosis		
Drug	Mechanism of Action	Suggested Dosage
Oxymetazoline HCl 0.1% (Upneeq)	α-adrenergic agonist, stimulation of the Müller's muscle	1 drop up to 2 times per day
Apraclonidine 0.5% (Iopidine)		1—2 drops up to 2—3 times per day
Naphazoline and pheniramine (Naphcon A)		1—2 drops up to 2—3 times per day *available over-the-counter*
Brimonidine Gel 0.33%		0.2 mg applied over the upper lid. Effect lasts up to 2 hour
Pyridostigmine Tablet	acetylcholinesterase inhibitor	60 mg PO up to 3 times per day for 2—3 wk. Effect lasts 6—8 hour per dose
Botox (onabotulinumtoxinA)	partially paralyzes a portion of the orbicularis oculi to aid in lid elevation	2—3 units of Botox in the pretarsal region 2 mm above the lash line

critical to understand that blepharoptosis can worsen if the toxin diffuses into the orbital septum. A more concentrated dilution is ideal in this scenario (Table 1) (Figs. 5 and 6).

Complications of dermal fillers

Dermal fillers are among the most popular non-surgical solutions for restoring lost volume, softening wrinkles, and enhancing facial contours. There are a multitude of dermal fillers in the market, with each one boasting distinct compositions and specific areas of application. They can be grouped in the non-permanent and permanent categories. The non-permanent group include calcium hydroxyapatite (Radiesse), poly-L-lactic-acid (Sculptra), hyaluronic acid (Restylane, Juvéderm), and collagen. The permanent group includes silicones, polyalkylimides, polyacrylamides, and polymethylmethacrylate (Bellafill, indicated for smile lines).]

The concept of dermal fillers appears to be very simplistic, injecting into areas where volume is deficient. Nevertheless, it

Fig. 5 Prior to injection of Botox in the pretarsal region, 1 to 2 drops of 0.5% of Tetracaine HCl is administered. Then, corneal shield with lubricant eye ointment is placed over patient's affected eye. (*From*: https://systane.myalcon.com/products/systane-nighttime/.)

is crucial to approach dermal fillers with extreme care, as complications, though infrequent, can occur. These potential issues encompass temporary swelling, bruising, infection, or localized lumps at the injection sites. In rarer instances, more severe complications, such as infection or vascular occlusion, may arise. To minimize these risks, it is paramount to understand the compositions and management for each type of filler that you provide for your patients.

Statistics

According to the American Society of Plastic Surgeons (2020), 3.4 million soft-tissue fillers procedures were administered, including both non-permanent and permanent fillers. The complication rates between these 2 groups greatly differ from each other.

From a group of 503 patients who received permanent fillers, 64.61% of patients experienced complications, with onset of symptoms occurred between 1 to 5 years (39.2%), less than 1 year (17.3%), followed by 6 to 10 years (12.61%).[11] The most common symptoms are lumps (64.6%), depression (58%), leathery skin changes (32.2%), granuloma formation (19.1%), and migration and translocation (4.2%). There are no established protocols for the treatment of permanent filler complications. Techniques ranging from disrupting the filler with subcision and transection, surgical removal, liposuction and ultrasound-guided removal, and the injection of triamcinolone or 5-Fluorouracil have been suggested. Due to the wide variability in onset and the types of symptoms present, the most effective means of averting complications associated with permanent fillers may entail refraining from undergoing such treatments altogether.

In contrast, non-permanent fillers are associated with different subset of complications. Although infrequent, they can be severe or permanent, including skin necrosis, vision loss, blepharoptosis, decreased visual acuity, ophthalmoplegia, or encephalitis have been reported. Local edema, skin erythema, headache, and local infection were most common.[12]

Fig. 6 After placement of corneal shield, the needle is injected from the lateral to medial approach, tangential to the curvature of the lid and 2 mm above the last line. Important to remain superficial to the orbicularis oculi.

Bruising

There is an increase in vascularity along the perioral and lip regions. Bruising and hematoma may occur when multiple injections are administered, especially for lip augmentation. The introduction of the cannula technique, however, has heralded a noteworthy reduction in the incidence of bruising and hematoma[13–19]. Patients now undergo a single precise entry point on each side, typically utilizing a needle of 2 to 3 gauges larger than the canula. This refinement has not only enhanced patient comfort but also witnessed an improved tolerance toward the procedure. Fig. 7 later demonstrates 1 way to perform lip augmentation and the nasolabial fold regions.

Temporary edema

Edema, a temporary inflammatory response, occurs more frequently when bruising is observed at the injection site. In the context of lip augmentation, especially when employing higher-concentration hyaluronic acid fillers like Juvéderm Ultra XC and Ultra Plus XC, lip edema frequently emerges

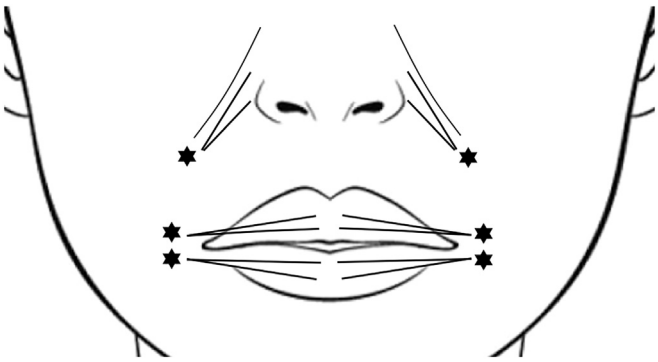

Fig. 7 Diagram illustrating the use of entry point for each side (star mark), using a needle 2 to 3 gauge larger than the canula to dilate the skin opening for easy insertion of the canula. Mild pressure is often required to go through the full half-length of the lip due to fibrous septations.

Table 2 Management of non-permanent filler complications

Adverse events	Onset	Suggested protocol
Tyndall Effect	Immediate	• Tear-trough region — inject 20—50 units of hyaluronidase with gentle massage • Lower face — puncture at the height of the concerned area with a 20-gauge needle, then attempt to express the filler with digital pressure
Contour Irregularities	Immediate	• Firm massage immediately after injection • Perioral region - apply pressure with second finger intraoral and thumb on skin in a circular motion • Advise patient to continue massaging at home
Granuloma	Months	• Triamcinolone 40 mg/ml mixed with 5-fluorouracil in a 1:1 ratio monthly (adjust dosage based on response) • Oral methylprednisolone 50 mg/day for 4 wk[22] • Oral antibiotics (clindamycin 300 mg bid and ciprofloxacin 500 mg tid) for 4 wk[22]
Pustules, vesicles, and abscesses	1—3 d	• Daily local wound care • Incision & drainage with abscess formations • Daily skin debridement with skin necrosis • Oral antibiotics Ciprofloxacin 500 mg bid for 10—14 d If allergic → Levofloxacin 750 mg daily for 10—14 d* Bactrim 800 mg/160 mg bid for 10—14 d If allergic → Doxycycline 100 mg bid for 10—14 d * Cross-reactivity between different generations of fluoroquinolones is uncommon, ranging between 2%—14%[23] Be cautious if hypersensitivity reactions include anaphylaxis
Delayed Hypersensitivity	Weeks to months	Presents as erythema surrounding the treated area • Ciprofloxacin 500 mg bid for 10—14 d or Levofloxacin 750 mg daily for 10—14 d and up to 6 wk • Alternatively, clarithromycin or azithromycin can be used * Avoid steroids and NSAIDS to decrease risk of biofilm formation
Vascular Occlusion	Immediate	Symptoms start with blanching of skin with pain, followed by livedo reticularis at day 1—2, pustules formation around day 3, coagulation of skin and ultimately skin necrosis (days after) • Massage the area and apply warm compress • Mark the area of skin erythema and take photograph • Inject 500—1500 units of hyaluronidase into the marked area of concerns with needle or canula A starting dose of 500 units per area is recommended (lip, nose, forehead). 1000 units if lip and nose are involved. • Reassess capillary refill time and skin color improvement Compare with unaffected side for baseline • Repeat hourly until resolution of symptoms • Close follow up and document with photographs • Consider oral antibiotics if skin discoloration and necrosis

Adapted from: Murray G, Convery C, Walker L, Davies E. Guideline for the Management of Hyaluronic Acid Filler-induced Vascular Occlusion. J Clin Aesthet Dermatol. 2021 May;14(5):E61-E69.

within 1 to 2 days post-injection, potentially persisting for up to 7 to 10 days. Patients, understandably, often express concerns and a desire for filler dissolution. Therefore, it is crucial to make sure patients apprehend the course. It is recommended to avoid modifying filler for at least the first 10 to 14 days after the proper placement of filler. This allows sufficient time for swelling and bruising to resolve fully before evaluating the outcome.

Infection

Infections account for approximately 15% of the rate of transient complications of non-permanent filler.[12] Pustules, vesicles, and abscesses were observed. The onset of symptoms typically starts between 1 to 3 days after the treatment. Management involves daily local wound care, incision and drainage, wound debridement if indicated, and oral antibiotics. A standard regime comprises of ciprofloxacin 500 mg twice daily for 10 to 14 days, and also considers doxycycline 100 mg twice daily or sulfamethoxazole/trimethoprim at 800 mg/160 mg twice daily if methicillin-resistant *Staphylococcus aureus* is suspected.[20,21] It is important to practice aseptic technique before administering treatment. Refer to Table 2 to access the comprehensive management protocol.[22,23]

Individuals with a prior history of herpetic outbreaks in the perioral region should be prescribed a prophylactic regimen of Valtrex at a dosage of 500 mg twice per day, commencing 3 days before the planned injection and continuing for a duration of 7 days following the procedure.

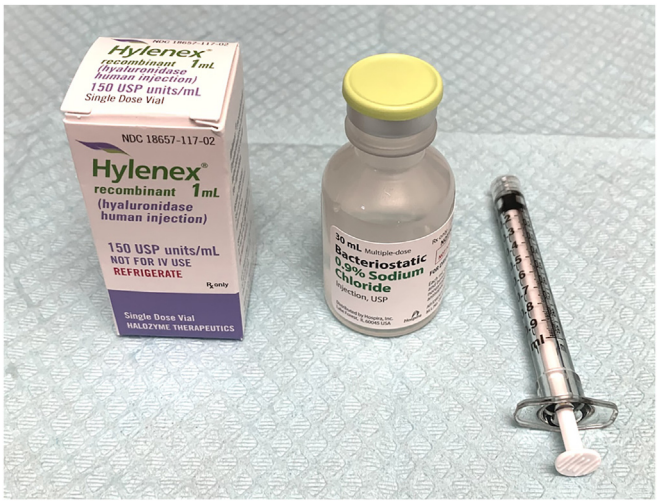

Fig. 8 Hylenex (human recombinant hyaluronidase) comes in a 1 mL vial. Diluting it with 2 mL of normal saline provides 50 units per mL mixture. Hylenex is recommended to be stored between 2 to 8℃. (*From*: https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=c3f1db01-58bf-2226-e053-2a95a90a8b33&type=display#:~:text=HYLENEX%20recombinant%20is%20indicated%20as,fluid%20administration%20for%20achieving%20hydration.&text=HYLENEX%20recombinant%20is%20indicated%20as%20an%20adjuvant%20to%20increase%20the,absorption%20of%20other%20injected%20drugs.)

Depth of injection

Tyndall effect arises when light shines through a colloidal mixture, a medium containing microscopically suspended particles, yielding a bluish discoloration due to the refraction of light. This often occurs with superficial injections of hyaluronic acid filler and more so in the thin-skinned area such as the tear-trough region. When the discoloration is faint, it can be mistaken for a bruise. Patient can be observed for 2 weeks if bruising is suspected. If there is no improvement or resolution, the hyaluronic acid filler can be dissolved with hyaluronidase to alleviate the bluish tinge of the Tyndall effect.

Hyaluronidase

Hyaluronidase is an enzyme that causes the degradation of both natural and crosslinked hyaluronic acid dermal fillers. The literature suggests 5 units of hyaluronidase recommended per 0.1 mL of 20 mg/mL hyaluronic acid filler. Some other studies suggest up to 30 units. Due to the wide range of suggested dosages, it is recommended to titrate to effect as the injected doses vastly differ from one region to another, as well as how much of the dermal filler we want to dissolve. Oftentimes, complete dissolution of filler is not necessary. Instead, as noted, hyaluronidase may be titrated to shape or mold the previously placed filler into a more desirable result. In cases of Hylenex (a human recombinant hyaluronidase) which comes in a 1 mL vial containing 150 units. The Aesthetic Complication Expert group[14] recommends a dilution in 1:2 ratio with either sterile water or saline, yielding a total of 3 mL. Some authors recommend diluting with local anesthetic to aid in patients' comfort. However, changing the pH of the constituents can alter the properly of the enzyme (Fig. 8).

Contour irregularities

Lumping of dermal filler occurs when too much filler is injected into a single site resulting in an unwanted palpable of visible accumulation of filler. Firm massage immediately after administering the filler is as important as the precise location of the injection. This is generally true regarding hyaluronic filler. Other dermal fillers, such as Sculptra, which is composed of poly-L-lactic-acid, works within the deep dermis to stimulate patients' own tissue to produce collagen. In turn, it enhances volumes, reduces wrinkles, and improves contours. Nodule formation is a late-onset complication of Sculptra. If a 3:1 dilution is used for injection, the occurrence rate is at 1%. The rate drops dramatically to 0.13% for a 5:1 dilution.[13] In addition, they need to be well mixed. Immediately prior to injecting Sculptra, we have the assistants continue the mixing process in the syringe until the injectors are ready. Hence, it is advised to use larger volumes of more dilute well-suspended Sculptra in order to reduce the risk of contour irregularities (Fig. 9).

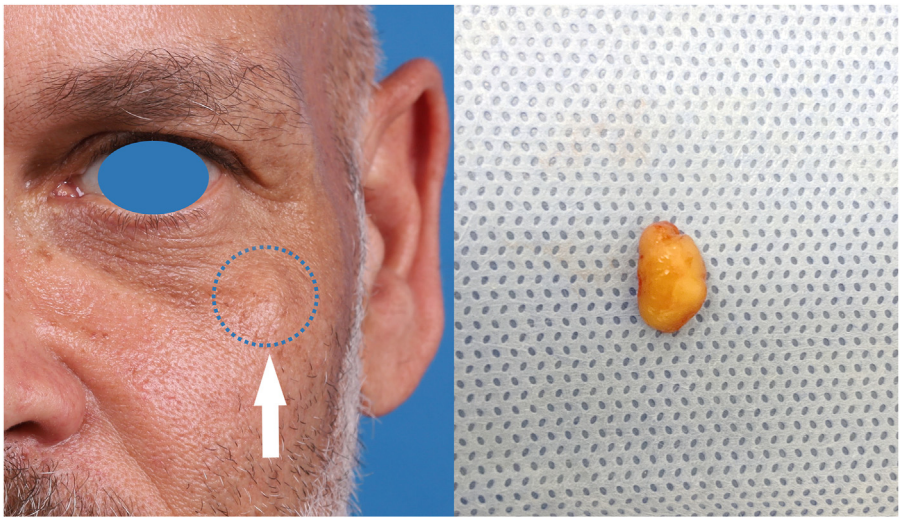

Fig. 9 This 58-year-old male received Sculptra injection into the cheek region to enhance volume. He returned to the clinic after 2 months, complaining of the lump under the skin over his left cheek. After recommending a period of monitoring and massage, the lump did not decrease in size. Thus, patient elected to have it excised. The nodule is shown on the right after removal through a small incision following his natural wrinkle crease.

Vascular occlusion

Vascular occlusion events occur when the target tissue does not receive adequate blood flow to the region. Mechanisms of extravascular compression, vascular spasm, and intravascular embolism were described, with the latter being best supported by evidence.[16] Extravascular compression arises when a large amount of highly viscous filler is injected next to a vessel, especially in areas with low distensibility, such as the nasal tip and nasal dorsum. Hyaluronic acid filler, when injected intravascularly, causes vessel wall inflammation and spasm. Resultant complications do not only occur with the embolus itself, but also as a result of spasm of the surrounding vascular structures. The main areas which have the highest risks of vascular occlusion are the glabellar region, nasolabial fold, nasal tip, and alar triangle.[17]

Signs and symptoms of vascular occlusion could present as immediate or of delayed-onset. Immediate signs and symptoms typically include pain and blanching, followed by reticulated erythema (livedo reticularis) in the distribution of the affected vessel. If this remains untreated, skin necrosis could entail. Filler embolism is another devastating complication associated with intravascular injection, particularly causing visual field deficits or stroke. This phenomenon is explained by retrograde flow proximal to the bifurcation of an artery or through valveless veins of the embolus.

Full resolution of complications can be observed if hyaluronidase is administered once signs and symptoms of impending skin necrosis are recognized early (<2 days).[15] The dosage of hyaluronidase varies and should be based on the amount previously injected and the anatomy of the affected area. Endpoint should be the complete resolutions of symptoms (capillary refill time or skin color has returned to baseline). For simplicity, on an hourly basis, a standard dose of 500 units is administered per area (lip, nose, and forehead) and gentle massage is performed to enhance the distribution of the enzyme.[18] The patient is kept for monitoring 2 to 3 hours after resolution of symptoms and is seen the following day.

Summary

The advent of neuromodulator and dermal fillers has transformed the realm of medical esthetics. They are readily available, provide immediate outcomes, and without downtime. As the annual count of procedures continues to climb, so too does the incidence of complications. Therefore, the significance of thorough training, a deep understanding of facial anatomy, expertise in managing complications, and delivering exceptional patient care cannot be emphasized enough.

Disclosure

Authors have no conflict of interest to declare.

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