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Complications of injectable fillers and neurotoxins

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ABSTRACT: All cosmetic injectable products are associated with the risk of both early and delayed complications. Early and expected side effects include swelling, bruising, and erythema at the injection. It is of utmost importance that patients are educated on the treatment they are consenting to receive and the potential risk of these therapies. Side effects of the various cosmetic injectable products, including both injectable neurotoxins and soft tissue fillers, are often technique associated, such as placing the filler too superficial or unintentional paralysis of facial muscles. Other complications, such as necrosis, intravascular injections, and infection may not be entirely technique-dependent, and must be managed swiftly and effectively. Finally, immunologic phenomena, such as delayed-type hypersensitivity reactions and foreign body granulomas, are complications that have no relationship to technique, and thus proper counseling and knowledge of management is required.

KEYWORDS: botulinum toxin, complications, injectables

Introduction

Cosmetic use of injectable fillers and neurotoxins is a growing field, with utilization of these products increasing annually. Neurotoxins and soft tissue fillers were the top two minimally invasive cosmetic procedures performed in 2009 according to the American Society of Plastic Surgeons. Botulinum toxin type A holds the number one top minimally invasive procedure with 4.8 million procedures in 2009, growing by 509% since 2000. Soft tissue fillers are second in minimally invasive procedures, growing with 1.7 million procedures performed in 2009, growing 164% since 2000 (1). The rapid growth in the use of these products is due to a number of factors, including versatility and creative placements beyond FDA indications, diminished social stigma surrounding their use, and a larger range of effective options available for cosmetic enhancements. In addition, these products have favorable safety profiles with rare AEs associated with their use. However, despite their impressive safety profiles, complications can and do occur. Given these are elective treatments, extreme care to prevent AEs by practitioners is paramount.

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Adverse events

AEs may occur with injectable products used for cosmetic purposes. Rarely, severe adverse events (SAEs) may occur. However, the probability of either of these events occurring is very small. Often times, normal or expected occurrences of injectables are confused as AEs. Normal occurrences with injections include bleeding, bruising, swelling, erythema, needle marks, asymmetry, skin lumpiness, and pain on injection.

AEs and SAEs would include scarring, hyper/hypopigmentation, infection, damage to deeper structures, visible tissue filler material, accidental intraarterial injection, vision loss, skin necrosis, granulomas, allergic reactions and hypersensitivity, migration of tissue filler or neurotoxin, chronic inflammation, lymphedema, or tissue stiffness.

In addition, an unsatisfactory result is always a possibility with cosmetic injectable products. The outcome may not meet the patients' expectations for improvement in wrinkles or soft tissue depressions. There is the possibility of poor or inadequate response that may be alleviated by additional injections. For other patients, surgical procedures or other treatments should be recommended in addition to the injectable treatment in order to meet their expectations.

Botulinum toxin

Injection of botulinum toxin (BTX) is utilized for treatment of hyperdynamic facial lines. BTX products are presynaptic nerve blockers that relax selected injected muscles. It is a fast, relatively noninvasive procedure that produces significant aesthetic improvement with minimal recovery. It is incredibly safe, with recent surveys indicating that greater than 80% found the treatment beneficial. The duration of effect lasts from 3 to 4 months (2).

Complications of cosmetic use are uncommon, with the majority of events being both mild and temporary. The most common complication following injection is ecchymosis. Other common short-term complications include pain, edema, purpura, short-term hypesthesia, short-term postinjection headaches, and infrequently, prolonged migraine headaches (3). Dysesthesia and purpura development may be minimized with careful use of preinjection topical anesthetic and the application of ice both before and after injection. Wearing loupes when injecting helps to indentify and avoid vessels especially in the periocular area. Postinjection headache can be categorized into to two types: minor and severe headaches. Minor headaches can be managed with standard over the counter analgesics, whereas severe headaches can be managed with stronger analgesics and systemic corticosteroids when necessary (4).

Typically, the majority of AEs related to BTX are due to improper injection technique rather than the neurotoxin itself. This is encouraging, as these AEs are thus preventable with complete knowledge of muscle anatomy and adequate training in technique. The remaining cases of AEs are due to local diffusion of injected BTX, leading to weakness of adjacent muscles. The radius of diffusion of BTX ranges from 1 to 3 cm from the injection site. Avoiding laser treatments that produce severe swelling on the day of BTX injections is beneficial to decrease the chance of diffusion to unwanted musculature. Reconstituting BTX with smaller amounts of dilutent will translate to smaller volumes per injection, and thus decreased local toxin diffusion and side effects (2).

Patient selection is critical in minimizing AEs with BTX. Absolute contraindications to BTX injection include known allergic reaction to any of the components of the formulation and preexisting infection at the injection site. Furthermore, BTX should not be administered to patients with unrealistic expectations or any degree of hesitation to treatment. Relative contraindications include preexisting neuromuscular conditions of the neuromuscular junction, peripheral motor neuropathies, women who are lactating, pregnant, or planning to become pregnant, patients with inflammatory skin conditions at the site of injection (such as psoriasis, contact dermatitis, and atopic dermatitis), and in patients with a history of previous lower eyelid surgery, as use of BTX in the periocular area in these patients carries risk of ectropion. In addition, BTX should not be administered to patients taking medications known to interfere with the neuromuscular junction, such as aminoglycosides, cholinesterase inhibitors, succinylcholine, curare-like depolarizing blockers, magnesium sulfate, quinidine, calcium channel blockers, lincosamides, and polymyxins (2).

A recently published report of AEs associated with BTX-A reported to the FDA revealed that 30 of the 1031 cosmetic cases were listed as serious potential complications, and included headaches, focal facial paralysis, muscle weakness, dysphagia, flu-like symptoms, and allergic reactions (4,5). No deaths were reported. Of the 995 cases classified as nonserious, the most common AE was lack of intended cosmetic effect. Other reported events included injection site reaction (19%), ptosis (11%), muscle weakness (5%), and headache (5%). Many clinicians would not consider focal facial paralysis and muscle weakness as AEs, as the therapeutic effect of BTX relies on these properties. In addition, lack of intended cosmetic effect may be due to judicious use of the BTX product, with intentional underdosing by the clinician in order to avoid excessive muscle paralysis with the option of offering touch-up at a later time.

Injection site reactions may include pain, erythema, edema, and bruising. Using smaller gauge needles, applying topical anesthetic 10–15 minutes prior to injection, and reconstituting the BTX with preservative-containing saline may all serve to lessen the pain on injection. In order to minimize bruising, patients should abstain from

aspirin for at least a week and NSAIDS for at least several days prior to treatment. Additionally, patients should avoid vitamin E and herbal supplements, especially those with known blood-thinning properties.

Postinjection headache associated with BTX has been studied extensively. In placebo-controlled trials, the incidence of headache among BTX is much lower than previously reported, because many patients receiving the placebo injection also complained of postinjection headache. Incidence of severe headache following treatment with BTX-A in a large series was 1%, with resolution of symptoms within 2–4 weeks among all patients. Should a patient experience a postinjection headache, appropriate analgesics should be offered, especially if the pain is not relieved by over the counter medications (3).

Depending on the muscle groups utilized for treatment, different potential adverse outcomes may occur. In the treatment of the forehead, the most common complication is brow ptosis. This is due to the frontalis being responsible for brow elevation. Avoiding BTX injection above the middle brow and or within 1 cm of the bony supraorbital margin will decrease the risk of brow ptosis. A less common complication of treating in the forehead region is upper eyelid ptosis due to downward diffusion of BTX into the eyelid levator muscle following injection of BTX at or above the mid-pupillary line. If this complication occurs, it can be alleviated symptomatically with eye drops containing alpha-adrenergic agonists such as apraclonidine or phenylephrine 2.5%. These drops may be applied to the affected eye until the symptoms resolve. A final potential complication of administration of BTX to the forehead is inadequate weakening of the lateral portion of the frontalis, leading to a lateral arching of the brow (FIG. 1). Injecting a small amount of BTX into the lateral frontalis should reduce this effect. Injection of the brow depressors simultaneously when treating the brows elevator will help decrease the risk of brow ptosis.

Administration of BTX to the glabella is associated most commonly with ptosis of the upper eyelid. The incidence of this complication has been reported to be as high as 5.4%, with most other studies finding the incidence to be less than or equal to 3% (6). This complication occurs most often due to improper injection technique by placing BTX deep with diffusion along the periostium. It may take 48 hours to 2 weeks for ptosis to develop, and may persist 2–4 weeks or even longer (FIG. 2A). Symptoms should be treated with eye drops containing alpha-adrenergic agonists as outlined previously (FIG. 2B).

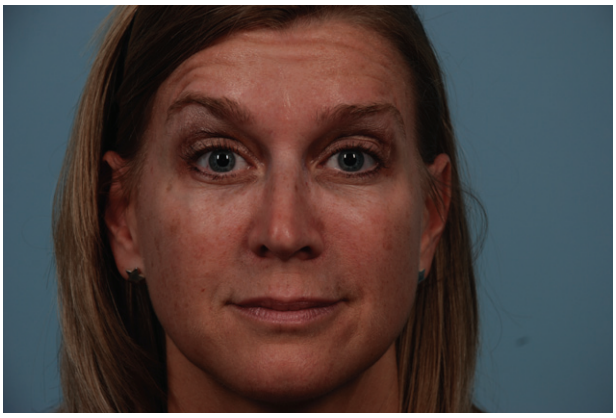

FIG. 1. "Cocked eyebrow" from residual lateral frontalis function.

The most common complication of BTX administration to the periocular area is bruising secondary to the rich and superficial vascular supply to this region. Superficial injection and generous ice application can both be beneficial. Other less common events that may occur for treatment of crow's feet include diplopia, loss of voluntary eye closure, and upper lip ptosis. Diplopia and loss of voluntary eye closure may be avoided by injecting BTX lateral to the orbital rim. Patients that develop diplopia should be referred to an ophthalmologist for management. Upper lip ptosis may occur by injecting BTX too close to the inferior border of the zygomatic arch or too deep, leading to weakening of the zygomaticus major muscle and subsequent upper lip ptosis. A "shelf"-like effect can occur if the units of toxin is not tapered down at the interior injection site.

Administration of BTX to the mid- and lower face should be performed with caution due to the highly variable muscular anatomy. Lower doses are recommended in this area. A common treatment in this area is to "bunny lines" caused by contraction of the upper nasalis muscle. Treatment can be complicated by ipsilateral lip ptosis secondary to weakening of the levator labii superioris. To prevent this complication, BTX should be injected high on the lateral nasal wall, above the nasofacial groove. In addition, treatment of the perioral area should be cautionary given the potential for an incompetent mouth. Injections into the orbicularis oris should be placed superficially and in small doses to prevent significant and asymmetric weakening of the lip sphincter.

A final common location for BTX administration for cosmetic purposes is in the neck for vertical

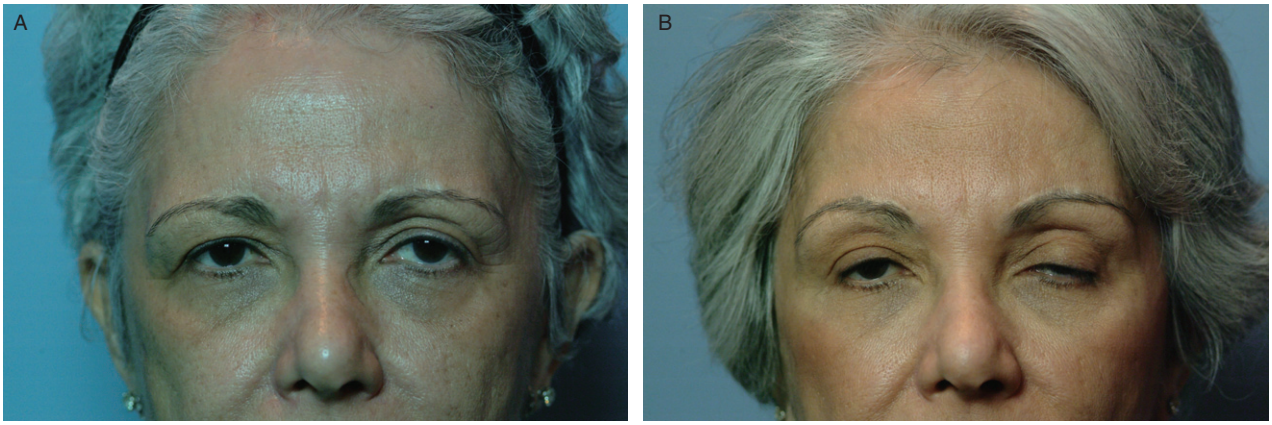

FIG. 2. **(A) Prebotulinum toxin A. (B) Ptosis postbotulinum toxin A injection for blepharospasm.**

platysmal bands. Clinicians must practice care to not inject too deeply and to use the lowest effective dose of BTX in this region. Diffusion or inadvertent injection of neurotoxin into the underlying sternocleidomastoid and laryngeal muscles can produce dysphagia, altered voice pitch, and weakness of neck flexors. The maximum recommended dose in this region ranges for 30–100 units of Botox™ (onobotulinum toxin A; Allergan Pharmaceuticals, Irvine, CA, USA) per session (2). The author favors using no more than 50 units per session with possible touch-up 2 weeks later. Thin female necks should be treated cautiously with 10 units onobotulinum toxin A per band or 25 units Abobotulinum toxin A per platysmal band to prevent symptomatic weakness. In patients with thin necks, no more than three bands at one sitting should be treated.

Due to the increased popularity and utilization of BTX, there has been concern of patients developing immunoresistance to BTX therapy. In theory, repetitive injections of BTX can lead to neutralizing antibodies to that particular neurotoxin, which translates to diminished therapeutic response. Investigators into this phenomenon have concluded a relationship to the amount of protein complexed with the neurotoxin and antigenicity. Since 1997, Allergan, the manufacturer of BOTOX, has decreased the protein load from 25 ng/100 units of neurotoxin to 5 ng/100 units, and the incidence of immunoresistance has fallen. Other factors thought to play a role in the development of immunoresistance include treatment dose and time interval between injections. Immunoresistance is much less of a concern with cosmetic applications of BTX than it is with therapeutic treatments in which a larger number of units is routinely needed.

Soft tissue fillers

Soft tissue fillers are utilized for various cosmetic purposes, from filling fine lines and wrinkles, to augmenting facial contour and projection. Replacement fillers, or temporary fillers, are filling agents that are injected into and occupy space for a variable period of time until they are either degraded by the body or naturally dissipate. Hyaluronic acid (HA) products, calcium hydroxyapatite (CaHA), marketed as Radiesse (BioForm Medical, Inc., San Mateo, CA, USA), and collagens comprise this category. Biostimulatory fillers, by contrast, operate by inducing neocollagenesis. These agents have either long-lasting or permanent effects. Poly-L-lactic acid (PLLA), marketed as Sculptra (Sanofi-Aventis US LLC, Bridgewater, NJ, USA), and polymethylmethacrylate (PMMA), marketed as Artefill (Suneva Medical Inc., San Diego, CA, USA), comprise this category.

Implantation of soft tissue fillers is a minimally invasive event. The gauge of the needle greatly contributes to the extent of superficial trauma experienced by the patient. The more viscous the filler, or the larger the particle size, requires a needle with a greater diameter, leading to a larger epithelial tear and greater disruption of dermal structures, with subsequent capillary leakage, edema, and stimulation of inflammatory cascades. In addition, the location of injection is associated with more or less local trauma. For example, implantation immediately above or beneath a muscle, such as in the lip or tear, trough sulcus has a higher propensity for swelling and bruising simply due to the highly vascular nature of these regions (FIG. 3).

Immediately following injection of a dermal filler, all patients should expect some degree of an

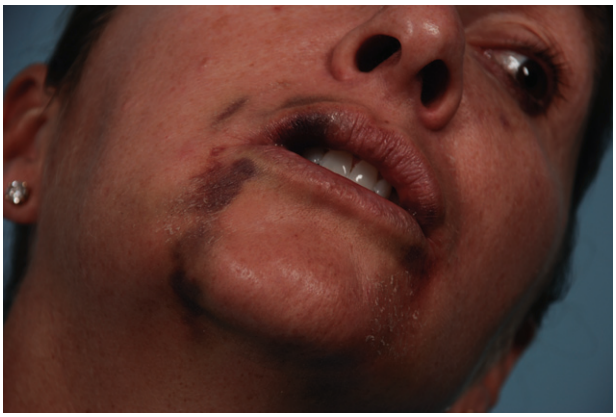

FIG. 3. Bruising 3 days posthyaluronic acid injection perioral rejuvenation and lip augmentation.

injection site reaction, such as needle marks, swelling, and bruising. In a randomized, double-blind, multicenter comparison of HA versus collagen for the treatment of nasolabial folds, injection site reactions occurred at a rate of 93.5% and 90.6% of the HA- and collagen-treated sites, respectively (7). Swelling and bruising at the injection site will be expected to persist to some degree for 4 to 7 days. Swelling and bruising can be minimized by avoiding aspirin compounds, nonsteroidal anti-inflammatory drugs (NSAIDs), and many vitamin supplements for 7–10 days prior to the procedure (8).

There are both technique-dependent and patient-dependent variables that contribute to the degree of these expected side effects. The degree of bruising in patients varies widely, and is worsened in patients that are on systemic medications or herbal supplements that are known to prolong bleeding time. The most common are medications that induce platelet aggregation inhibition and coagulation factor deficiency, both of which can increase postsurgical bruising. In addition, patients may have inherent disorders of platelet aggregation or coagulation factors that are often not diagnosed until after a surgical event. Swelling may also occur, and this is often mediated by the inflammatory cascade that is activated by the trauma to the dermal structures during injection. Pre-treatment and posttreatment with ice can decrease the swelling and bruising response associated with cosmetic filler injection (9).

Hypersensitivity reactions are a risk with many of the dermal fillers. The risk is highest with those products that contain bovine collagen, but is a theoretical risk with any of the dermal filling agents. Classification of hypersensitivity reactions is difficult, not only because clinically the reactions do not have a unique morphology, but also because these reactions are rare for most fillers, causing most of our information to be drawn from sporadic case reports. Defining a hypersensitivity reaction versus an allergic reaction versus an abnormal response has largely been based on magnitude of response. Swelling and induration are normal and expected after filler injections; however, if this response is more exaggerated or longer in duration, the physician may consider the circumstance to be abnormal. With the exception of an indisputable case of immediate, massive angioedematous response to a replacement filler (FIG. 4A–C), classification of these cases as hypersensitivity reactions or allergic reactions poses a significant challenge. Furthermore, defining the etiologic agent can be equally elusive (10).

Hyaluronic acid

HA agents are temporary fillers that are injected and occupy space for a period of time prior to being either degraded by the body or naturally dissipating. HA is a naturally occurring molecule that tends to be identical across species, theoretically making allergy to the product a negligible concern. Prior skin testing is therefore not indicated. Some HA products are derived from avian sources, but the agents available in the United States for cosmetic use are derived from a bacterial source (nonanimal stabilized HA, NASHA) and therefore should not elicit an allergic reaction in patients who are sensitive to beef, chicken, and eggs. However, HA may contain varying amounts of hyaluronin-associated proteins, which may explain why sensitivity reactions have been reported (11).

There have been case reports of acute hypersensitivity reactions to HA products. Lupton and Alster reported a case that occurred after the third treatment that they felt was most likely due to an impurity in bacterial fermentation (12). The patient manifested clinically with multiple tender red nodules, and no pathogenic bacteria was cultured from the nodules. In 2002, Friedman et al. reviewed the worldwide AE data for NASHA, including manufacturers' data from 1999 and 2000 (13). In 1999, of 144,000 patients, there were 104 cases of hypersensitivity reported (incidence 0.7%), and in 2000, of 262,000 patients, there were 52 cases of hypersensitivity reported (incidence 0.02%). Hypersensitivity cases were defined as swelling, erythema, and tenderness shortly after injection. The decline in incidence of hypersensitivity reac-

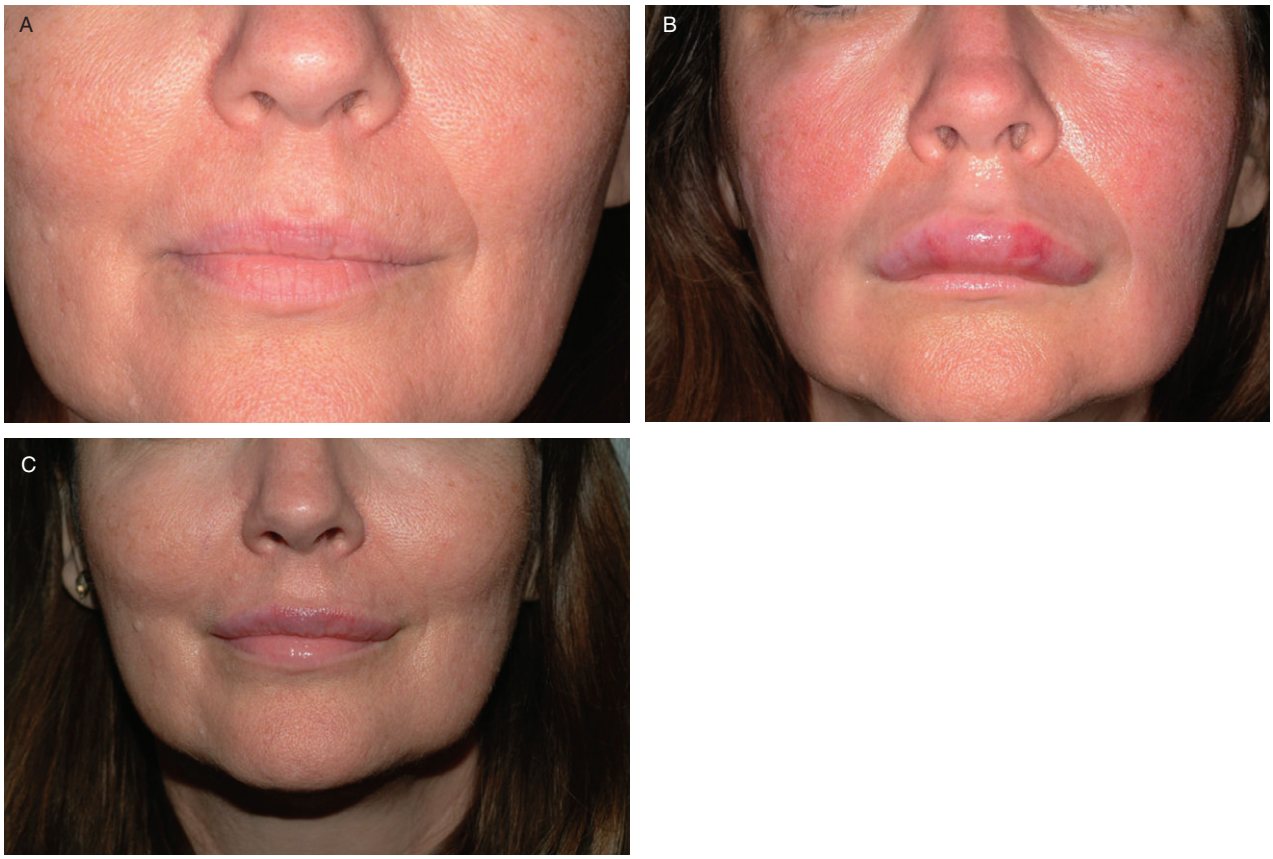

FIG. 4. (A) Prelip augmentation. (B) Angioedema immediately after hyaluronic acid injection. (C) 12 days posthyaluronic acid lip augmentation.

tions from 1999 to 2000 was attributed to changes in the processing of NASHA to decrease trace protein present in the formulation. Whether these cases represent true allergy or stimulation of direct mast cell degranulation has yet to be elucidated. Overall, hypersensitivity to NASHA and avian-derived HA is rare and self-resolving.

The primary mechanism of action of HA products is that they absorb and hold water. The saturated formulations provide a 1 : 1 volume correction, and once injected, the volume will not increase further. The anhydrous formulations, however, are designed to absorb water from the body, and the initial volume therefore increases after injection (14).

Both saturated and anhydrous formulations are clear, colorless, viscous gels. When these products are injected too superficially, they can produce a phenomenon known as the Tyndall effect (also referred to as the Rayleigh effect), causing a bluish discoloration at the site of injection. This effect may occur at any location of injection, but is most common in the thin skin of the lower eyelids (FIG. 5). The clinician's apprehension to place the filler on the periosteum results in a higher risk for these visible papules. The bluish bumps created by this complication are resistant to the normal process of degradation that occurs with HAs, therefore watchful waiting may not be an optimal option. The best treatment for resorption of these visible papules is with the use of hyaluronidase

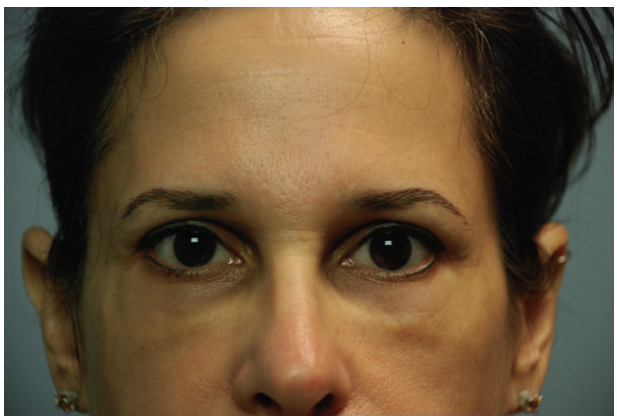

FIG. 5. Fullness in lower lids from hyaluronic acid placement too surperficial.

FIG. 6. **(A) "Tyndall effect." (B) Dissolutions of the "Tyndall effect" after placement of hyaluronidase.**

(FIG. 6A,B). Hyaluronidase is a soluble protein enzyme that acts at the site of local injection, and breaks down and hydrolyzes HA by splitting the glucosaminidic bond of glucuronic acid. Subsequently, the viscosity is decreased, promoting diffusion and absorption (10). Resolution should be expected within 2 days of injection. After injection of hyaluronidase, recommendations are to massage the area to facilitate absorption (15). An appropriate dose is between 30 and 50 units of hyaluronidase. Other options include nicking the papule with a no. 11 blade and expressing the product out with a comedone extractor.

There is a rare risk of sensitivity to the animal-derived hyaluronidase enzyme. Therefore, a preliminary skin test should be performed on the patient prior to its use. Three units of hyaluronidase product should be injected intradermally, and the site be observed for at least 20 minutes or even overnight. A local wheal-and-flare is consistent with a positive reaction (16).

There is a small chance that the bluish discoloration that developed after treatment with HA may represent traces of hemosiderin deposition associated with vascular injury on injection. In this circumstance, hyaluronidase should not be expected to improve the discoloration (17).

Local complications, such as swelling, bruising, and erythema, are common with HA, as is pain on injection. Products that do not contain lidocaine may require local or dental blocks for patient tolerance. In addition, increased bruising may be noted with injection of HA due to its similar structure to heparin (18).

Calcium hydroxylapatite

Calcium hydroxylapatite (CaHA), marketed as Radiesse, is a biostimulatory dermal filler composed of synthetic CaHa microspheres suspended in carboxymethylcellulose, an aqueous carrier gel. The microspheres are identical in composition to the mineral portion of human bone and teeth (19). Because these components occur naturally in the body, they are therefore inherently biocompatible. In addition, CaHA does not contain animal or human tissue derivatives, making sensitivity testing unnecessary.

Pain on administration of CaHA is significantly reduced by mixing CaHA with 0.2–0.4 mL of 2% lidocaine, administered with 1.3 mL syringes. Furthermore, the viscosity and extrusion force to inject the product is also significantly decreased with this dilution (20,21).

Administration of CaHA provides immediate 1 : 1 correction, and does not expand beyond what was injected. Over time, the carrier gel is absorbed and local histiocytic and fibroblastic responses produce new collagen around the microspheres. The result is a longer lasting implants with characteristics close to natural tissue. Longevity of correction ranges from 10 to 18 months, depending on the study reviewed.

A common complication of CaHA are visible white nodules, most often occurring in the lip mucosa. In this location, palpable nodules occur at a rate of 11.6% (22). Therefore, CaHA is not recommended for lip augmentation. In addition, it should be administered with caution to the tear trough region. In general, the overall rate of nodule formation with CaHA is very low, and no granulomas or nodules have been reported when the product is injected into areas other than the lips (23). If visible nodules do occur, these can be treated by puncturing the nodules with a no. 11 blade or needle, and then expressing the contents (8).

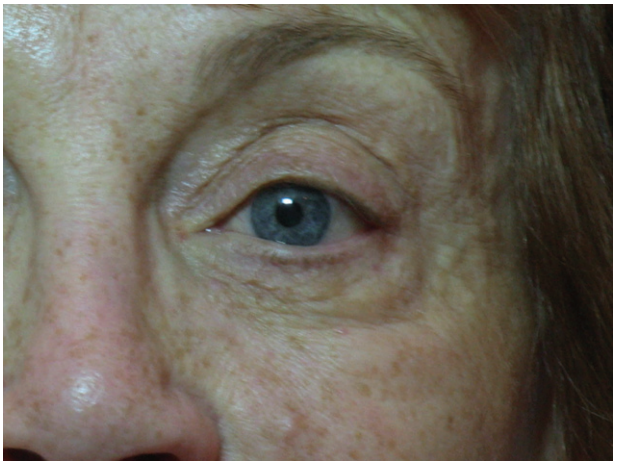

FIG. 7. Periocular nodules from Sculptra injections.

Poly-L-lactic acid

Poly-L-lactic acid (PLLA), marketed at Sculptra, is a biostimulatory filler that is a biocompatible synthetic polymer derived from the alpha-hydroxy acid family. PLLA stimulates a host response that may vary in degree depending upon how much is administered, where it is injected, and the manner in which it is applied. The goal of this product is to stimulate a subclinical inflammatory response that is followed by subsequent encapsulation of the microsphere, and finally fibroplasia. Due to the extensive biostimulatory effects of this product, it is considered a semi-permanent filler.

Early studies in treatment of patients with HIV-related lipoatrophy revealed that AEs occurred in patients in which too much product was injected at too short of intervals, leading to a more vigorous host response than was desired (24). Technical considerations to avoid overcorrection are recommended, such as using less product with fewer treatment sessions in younger, fuller faces.

Another common finding with this product are palpable, but usually nonvisible subcutaneous "micronodules." (FIG. 7). These nodules may occur in as many as 44% patients receiving this product, and spontaneous resolution is expected to occur in 27% by 96 weeks (17). These micronodules are thought to be due to the development of a fibrous reaction to the presence of the implant, and occur at an average of 7 months posttreatment (range 0.3–25 months) (25).

More recent studies of PLLA using a diluted suspension of the product have resulted in a dramatically decreased rate of micronodule formation. In a review of 200 patients treated with PLLA diluted in 4 mL of SWFI and 1% lidocaine resulted in a rate of micronodule formation of <5% (17). Many practitioners use 6 cc of sterile water for reconstitution, and in areas such as the hands and chest, even larger dilutions are used. Longer reconstitution times are also recommended, with reconstitution occurring at least 8 hours prior to injection of the product (8). Care should be taken to inject the product in the superficial fat and not in the middermis, and the clinician should be careful to not inject the precipitate at the end of the syringe.

There has been a recent report of three cases of foreign-body induced granulomatous reactions occurred after injection of PLLA. It has been theorized that these reactions occurred due to aberrant reactivity of the recipient to the material (26). This raises a concern among practitioners regarding the use of PLLA, given most of the data for its use has been on the HIV-positive population, and thus the risk of an immune response to this product among immunocompetent individuals is still not well established.

Polymethylmethacrylate

Polymethylmethacrylate (PMMA), marketed as Artefill, is a biostimulatory permanent filler composed of nonresorbable microspheres suspended in a carrier gel. The gel vehicle is composed of 3.5% bovine collagen, 92.6% buffered isotonic water, 0.3% lidocaine, 2.7% phosphate buffer, and 0.9% sodium chloride. PMMA provides a scaffold for human collagen deposition (14). A number of AEs have been reported with this product, including local tissue necrosis, granuloma formation, chronic inflammation, and infection. A unique complication associated with this product is the development of stiffness, lymphedema, and nodules after treatment of the lips (27).

Skin testing is mandatory prior to use of this agent, and PMMA is contraindicated in patients with either one positive response or two equivocal responses. Furthermore, contraindication is extended to patients with a history of severe anaphylaxis, those with an allergy to bovine collagen or sensitivity to lidocaine. Product sensitivity may also be associated with the development of delayed granulomas, although the rate is low at just 0.01%. These tend to occur from 6 to 24 months posttreatment, although there are reports of them developing as late as 5 years postinjection (15). Treatment includes intralesional corticosteroids, progressing to higher concentrations as needed (8).

PMMA has also been reported to cause complications if placed too superficially, leading to lumps

and bumps of excessive product. In addition, there have been reports of persistent pruritus and redness, which can be treated with topical or intradermal corticosteroids (28). Finally, placement of excessive product too superficially has resulted in hypertrophic scarring. This can be treated with repeated intralesional corticosteroid injections (starting with IL TAC 10 mg/mL with increasing concentrations of 20, 30, and 40 mg/mL progressively if needed at 4-week intervals) (8). It is therefore not recommended in patients with a susceptibility to either keloid or hypertrophic scarring. It is not indicated for lip augmentation.

It is recommended to first bring PMMA to room temperature prior to injection, and that proper technique includes passing the needle two or three times prior to placement of small subdermal strands of product in the deep dermis. A 26-gauge needle is considered optimal for injection, and conservative administration is of utmost importance, considering removal of product requires excision. The incidence of granuloma formation has been reportedly small, at just 0.3% (29,30), and will often resolve with intralesional corticosteroid injections (31).

Adverse events to dermal fillers

In general, AEs related to injectable agents remain relatively unusual. The occurrence of adverse reactions often relates to both the inherent properties of the product and the technique of injection or dilution of the filler. The technique of injection can create complications if the product is administered at the inappropriate skin depth, leading to skin changes or excessive lumps; at the improper location, leading to product misplacement; or in the improper volume, leading to contour deformity and/or palpable lumps.

Persistent erythema and telangiectasias that continue beyond 2 weeks after injection may occur with any of the dermal fillers. If this occurs in areas treated with HA, they can be treated with hyaluronidase (32). Erythema and telangiectasias after filler injection have also been treated successfully using the 532-, 595-, or 1064-nm laser. Several treatments with laser may be required for optimal cosmetic result (33).

All dermal fillers induce some form of histologic soft-tissue reaction that evolves over time. Therefore, granuloma formation can occur with any of the injectable dermal fillers. Additionally, because subclinical granulomatous inflammation is a normal tissue response to injected materials, clinical significance is based on the extent, severity, and long-term progression. Fillers that contain alloplastic materials have shown a higher propensity for granuloma formation (18), and the risk of granuloma formation occurs less frequently with resorbable implants as compared with more permanent products.

Treatment of granulomas is typically through administration of local or systemic corticosteroids. Prednisone in doses up to 60 mg/day has been reported to improve patient signs and symptoms (17). Another approach is to discourage aberrant cell growth by injection of 5-fluorouracil plus corticosteroids (28). For well-circumscribed nodular granulomas, surgical excision is the most effective and definitive approach.

Nodule formation tends to occur as a late adverse reaction from implantation of a filler. Nonerythematous nodules that develop immediately after injection occur as a result of uneven distribution of the product. Infection may present clinically as single or multiple nodules, often with associated signs of inflammation, such erythema and tenderness. In addition, nodules secondary to a hypersensitivity reaction can present identically to those due to infection, and should be treated as infectious until a diagnosis of hypersensitivity has been established through thorough skin testing.

Necrosis

Necrosis due to injection is a rare but potentially devastating severe AE associated with soft tissue fillers. Necrosis typically occurs due to either interruption of vascular supply due to compression, or frank obstruction of vessels by direct injection of the material into a vessel (FIG. 8). The glabellar region carries the greatest risk of necrosis, presumably because the small-caliber vessels branching from the supratrochlear arteries to supply this region have minimal collateral circulation.

An additional risk from intravascular injection in the glabellar region is blindness. This catastrophic complication occurs from the injected filler flowing in a retrograde fashion to the retinal artery. There is an increased risk of this event occurring when a large volume bolus is injected, such as greater than 0.1 mL of material. Of all the dermal fillers, PMMA carries the greatest risk of this complication (15).

A number of precautions should be taken to avoid necrosis. These precautions include knowing the anatomy of the vasculature in the injection area, aspirating prior to injection, not using exces-

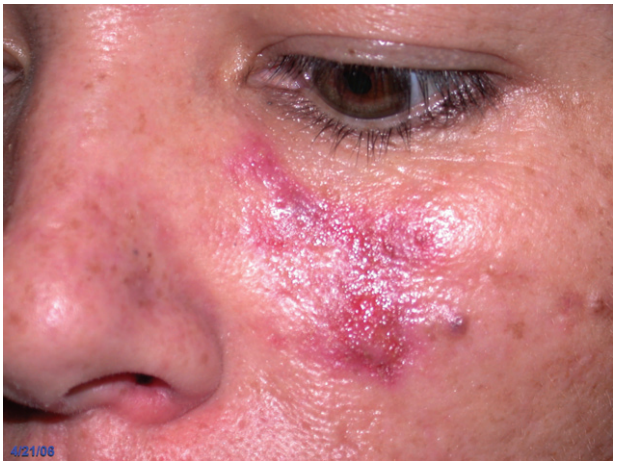

FIG. 8. Erosion following intravascular injection of hyaluronic acid filler to acne scars.

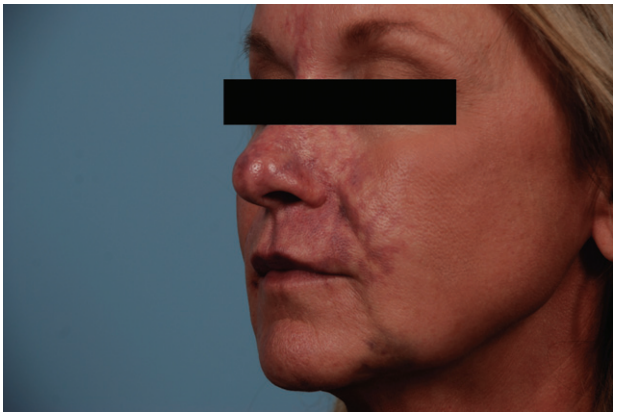

FIG. 9. One day postintravascular occlusion of the angular artery.

sive volume of the product, and not using excessive pressure during the injection (34). If necrosis is suspected, treatment options include the application of warm clothes in order to facilitate local vasodilation, and the application of nitroglycerin paste – at the first sign of blanching – to promote further vasodilation. For cases in which an HA filler was employed, there has been a report of impending necrosis being successfully treated after injection of hyaluronidase along the distribution of the underlying vessel and adjacent violaceous skin. In this case, it is thought that the hyaluronidase removed some of the product and decompressed the vessel (35). Therefore, it is recommended to inject the affected area with hyaluronidase if intravascular injection is suspected, with 75–100 units of the product (FIG. 9). There is some evidence to suggest that using hyaluronidase for impending necrosis, even if the dermal filler used was not an

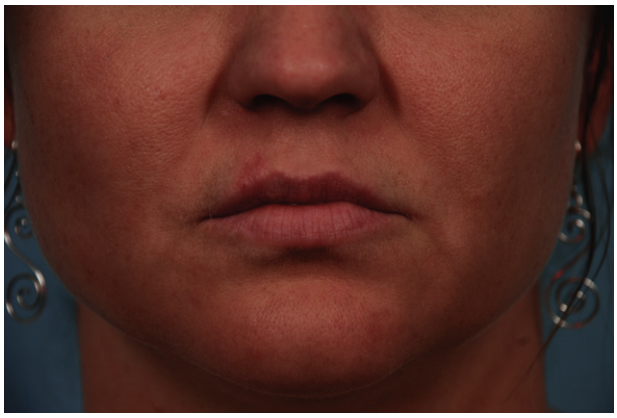

FIG. 10. Patient with herpes simplex virus of the upper lip.

HA. The theory in this context is that the hyaluronidase may disperse the other material as well, allowing for revascularization (15). For severe or unresponsive cases of necrosis, deep subcutaneous injections of low-molecular-weight heparin into the affected area may be of benefit (36).

Gentle debridement and application of ointment to the necrotic skin is also recommended. In cases of tissue loss, no reconstruction should be employed for several months, or at least until the eschar has fallen off and normal circulation and tissue integrity have been restored (37).

Infection

Several infectious disease concerns have been associated with soft tissue fillers. The first is that these fillers may trigger recurrent herpes infection in patients with a history of herpes outbreaks. Therefore, patients with a history of herpes labialis lesions should be given prophylactic antiviral treatment prior to lip augmentation (38). Patients with active herpes lesions should not receive injections until the lesions have completely resolved. Occasionally, patients may have an outbreak of herpes labialis after treatment of the lips, especially if they have no known history of herpes infection (FIG. 10). Treatment with Valtrex is recommended. If secondary impetiginization is present, Keflex should be added to the regimen (15).

Infection due to contamination is another concern. In 2002, there was an outbreak of *Mycobacterium abscessus* infection following injection with an unapproved HA product called Hyacell. The product was administered by a woman posing as a physician, and the product was non-FDA approved and was illegally brought to the United States from South America.

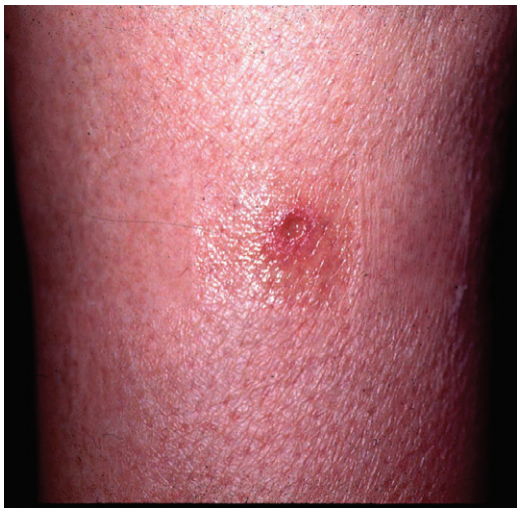

FIG. 11. A typical mycobacteria (courtesy of Dr. Phil Eichorn).

However, infections can potentially occur using licensed products in the hands of experienced physicians. Inflammatory nodules that occur within 3–14 days of injection should be treated as infections. These nodules are typically red, painful, and tender. If there is any fluctuance or impending skin erosion, immediate incision and drainage with culture should be performed (FIG. 11). Sending tissue rather than aspirate for culture is preferred, and although streptococcal and staphylococcal species are expected to predominate, the material should be sent for aerobic and anaerobic culture. Patients should be initiated on broad-spectrum antibiotics, such as a tetracycline plus a macrolide, to limit the emergence of resistant bacteria. Other antibiotic regimens include clarithromycin, quinolone, and minocycline, often for as long as 4–6 weeks to cover for atypical mycobacterial infection, which may not grow well in culture (15). Reevaluation of the site should occur after 48 hours of antibiotic therapy, and if fluctuance continues, incision and drainage and repeat culture should be sent. If no response to therapy occurs over several days, a biopsy for tissue culture and an adjustment of antibiotics should be considered (32).

When there are multiple inflammatory nodules, especially when arising in multiple sites corresponding to the injection sites, contaminated product should be suspected. The recommended management is the same as employed for solitary inflammatory nodules, including incision and drainage, culture, and empiric antibiotics (15).

A recent concern as a source of bacteria in cases of infection associated with soft tissue fillers is biofilms that are present on dental plaques. Biofilms are complex aggregates of microorganisms that excrete an extracellular encapsulated protective adherent matrix, making them highly resistant to antimicrobials. These may be present on dental plaques, making intraoral injection of soft tissue filler carrying higher risk of secondary infection from these highly antibiotic-resistant bacteria. Further risk is thought to occur when injection occurs soon after a dental procedure, which may disrupt the biofilm and increase the amount of circulating bacteria (15).

In order to optimally prevent injection site infection, recommendations are as follows: properly sterilize the treatment area with either alcohol or chlorhexidine, never inject over areas of active injection, such as acne, herpes simplex, or impetigo, avoid intraoral injection, avoid injecting over an existent implant, and avoid injecting in patients whom have undergone a recent dental procedure (15).

Conclusion

The use of injectable products for cosmetic enhancement is increasing rapidly. This is due in large part to the wide range of effective options, decrease in social stigma, and the excellent safety profile garnered by these products. However, complications do occur, and therefore an awareness of the potential complications, as well as how to best avoid or manage them, will help maximize the success of these important therapeutic tools.

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