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Complications of hyaluronic acid fillers and their managements

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Abstract

Background: Injection of dermal fillers is one of the most commonly performed procedures in the cosmetic dermatology practice. As its usage is expanding, the possibility of complications will likely increase.

Objective: To review and summarize the complications associated with hyaluronic acid injections, and to provide a guide to avoiding them and managing these complications if they do occur.

Methods: A comprehensive PubMed and Google scholar electronic database search was performed (2005–July 2015). A total of fifty-five articles were selected and included.

Results: Most of the complications associated with hyaluronic acid filler use are mild, transient and reversible. Serious complications due to vascular occlusion include cutaneous necrosis and blindness, which although rare can occur due to the compression of the vessel or direct intravascular injection.

Conclusion: Injection related side effects are the most commonly seen, which are usually transient. Vascular occlusion is the most severe complication associated with hyaluronic acid filler injection. A thorough understanding of the facial vascular anatomy reduces the risk of vascular occlusion. Early identification of a vascular occlusion and a prompt intervention can significantly decrease the risk of long term sequelae. Guidelines to avoid, identify and manage different hyaluronic acid filler complications have been suggested.

Keywords: Dermal fillers; Facial rejuvenation; Hyaluronic acid; Complications

Contents

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1. Introduction

Injection of dermal fillers is one of the most commonly performed procedures in cosmetic dermatology practice. According to recent data published by the American Society of Plastic Surgeons (ASPS) in 2014, soft tissue filler injections increased by 253% since the year 2000 with 3% increase from the year 2013 (2.3 million). Hyaluronic acid (HA) fillers constituted 78.3% of all injectable dermal fillers with 7.5% increase from the previous year (American Society of Plastic Surgeons, 2014). Compatibility of HA with the human body and reversibility of injected HA using intralesional hyaluronidase enzyme make HA based dermal fillers favorable for many injectors.

As the usage of dermal fillers is expanding, complications will likely increase. Even in the hands of an experienced injector, various complications can occur. Fortunately, most of the complications associated with HA fillers are mild, transient and reversible.

Injection technique related adverse effects are the most commonly seen. Maximizing injection technique and thorough understanding of potential complications and their management can help avoid, identify and manage them when they do occur.

2. Hyaluronic acid fillers

HA forms an integral part of the natural extracellular matrix which is found in high amounts in several connective tissues including the skin, the vitreous humor of the eye and the synovial fluid (Stern and Maibach, 2008). Chemically, HA is a linear polysaccharide composed of repeating disaccharide units of glucuronic acid and *N*-acetylglucosamine (Sudha and Rose, 2014). HA is considered to be the most popular dermal filler to replace volume loss due to normal aging for several reasons including: its hygroscopic property, biocompatibility and reversibility. Over the past several decades, various forms of HA fillers have been developed and they differ in many aspects including: the type and degree of crosslinking, gel viscosity, gel hardness, gel consistency, extrusion force, total HA concentration and duration of presence in the skin (Tezel and Fredrickson, 2008). Different FDA HA filler products are shown in (Table 1).

3. HA fillers complications

HA filler complications can be divided into early and delayed onset complications according to the time of appearance of symptoms and signs. Early onset complications typically appear hours to days post procedure while delayed onset complications usually develop weeks to years post HA filler injection (Table 2).

4. Injection site adverse effects

The most common side effects associated with HA injection are local injection related side effects which manifest as edema, pain, erythema, itching and ecchymosis (Lafaille and Benedetto, 2010). These adverse side effects are mild and usually last less than one week.

Pain is considered to be a common adverse effect during HA injection. Several techniques can be used in order to minimize the pain associated with injections, which include: the utilization of the small needle gauge or blunt-tipped cannulas, the use of topical anesthetic agents, application of ice prior and after injection, vibratory distraction and nerve blocks (Jean Carruthers, 2013).

Ecchymosis and edema can be minimized by stopping the intake of aspirin, NSAID, supplements containing ginkgo biloba, vitamin E, omeg-3, fish oil, ginseng, kava–kava and St John's wort at least one week prior to the procedure (Gilbert et al., 2012). Before and after procedure use of arnica, topical vitamin K or bromelin may decrease the post-injection ecchymosis, but no controlled studies prove their effectiveness (Jones, 2010). Some practitioners use the vascular laser to reduce post-injection bruises (Jean Carruthers, 2013).

The Tyndall effect is caused by placing the HA fillers too superficially and it manifests as bluish discoloration, which can be treated by injecting 15–50 IU of hyaluronidase followed by massage (DeLorenzi, 2013).

5. Hypersensitivity reactions

Safety data on non-animal-derived hyaluronic acid (NASHA) gel show that it has a favorable safety profile. One study on the use of NASHA found that localized hypersensitivity, which was defined as "swelling, erythema,

Table 1
U.S FDA* approved HA fillers.

Product	Active content	Manufacturer	Date of approval	Approved indications for usage
RESTYLANE INJECTABLE GEL	Hyaluronic acid	Q-med Ab	2003	Injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds)
HYLAFORM (HYLAN B GEL)	Modified hyaluronic acid derived from a bird (avian) source	Genzyme Biosurgery	2004	Injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds)
CAPTIQUE INJECTABLE GEL	Hyaluronic acid	Genzyme Biosurgery	2004	Injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds)
RESTYLANE INJECTABLE GEL	Hyaluronic Acid	Medicis Aesthetics Holdings, Inc	2005	Injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds)
JUVEDERM 24HV, JUVEDERM 30, and JUVEDERM 30HV	Hyaluronic Acid	Allergan	2006	Use in mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds)
ELEVESS	Hyaluronic Acid with Lidocaine	Anika Therapeutics	2006	Use in mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds)
PREVELLE SILK	Hyaluronic Acid with Lidocaine	Genzyme Biosurgery	2008	Injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds)
RESTYLANE INJECTABLE GEL	Hyaluronic Acid	Medicis Aesthetics Holdings, Inc	2011	Lip augmentation in those over the age of 21 years
BELOTERO BALANCE	Hyaluronic Acid with Lidocaine	Merz Pharmaceuticals	2011	Injection into facial tissue to smooth wrinkles and folds, especially around the nose and mouth (nasolabial folds)
RESTYLANE-L INJECTABLE GEL	Hyaluronic Acid with Lidocaine	Medicis Aesthetics Holdings, Inc.	2012	Injection into the mid to deep dermis for correction of moderate to severe facial wrinkles/folds (such as nasolabial folds) and for lip augmentation in those over the age of 21 years
JUVEDERM VOLUMNA XC	Hyaluronic Acid with Lidocaine	Allergan	2013	Indicated for deep (subcutaneous and/or supraperiosteal) injection for cheek augmentation to correct age-related volume deficit in the mid-face in adults over the age of 21
RESTYLANE SILK	Hyaluronic Acid with Lidocaine	Valeant Pharmaceuticals North America LLC/ Medicis	2014	Indicated for lip augmentation and dermal implantation for correction of perioral rhytids (wrinkles around the lips) in patients over the age of 21

* United States Food and Drug Administration.

Table 2
Classification of HA fillers complications.

Early onset adverse effects (Hours to days post procedure)	Delayed onset adverse effects (weeks to years post procedure)
Injection site reaction	**Biofilms**
Edema	**Foreign body granuloma**
Pain	**Dyspigmentation**
Erythema	**Scarring**
Itching	
Ecchymosis	
Hypersensitivity reaction	
Infection	
Herpes simplex virus infection	
Abscess/cellulitis	
Mycobacterial infection	
Tyndall effect	
Surface irregularities and nodules	
Vascular occlusion	
Local tissue necrosis	
Embolization of blood vessels (blindness, stroke)	

and induration at the implant site, sometimes with edema in the surrounding tissue with a median duration of 15 days", occurred in only 1 of every 1400 patients. Another study found only a 0.8% incidence of acute or delayed hypersensitivity reactions to NASHA gel (Leonhardt et al., 2005).

NASHA may contain immunogenic protein, potentially introduced through the manufacturing process. Hypersensitivity reactions to Restylane (Medicis Aesthetics Inc.) documented in the 1990 s are believed to have been related to protein contaminants. The reduction in the frequency of hypersensitivity reactions since the year 2000 may be partly explained by the introduction of a hyaluronic raw material with trace amounts of protein six times lower than the raw material previously used (Van Dyke et al., 2010). Leonhardt et al. (2005) reported a case of angioedema hypersensitivity reaction following the injection of Restylane in the upper lip. This patient, however, was treated with a systemic corticosteroid.

6. Infections

Injectable fillers are also associated with infections, which can result from the breach in skin surface integrity. The infectious agents may be bacterial, viral or fungal. In order to minimize the risk of infection, the patients' history should be taken, including any history of recent dental procedures, any periodontal treatment planned within the next two weeks or any history of chronic sinusitis. The patient should not wear makeup either before or immediately after the procedure. Aseptic technique should be used, including proper skin sterilization with 2–4% chlorhexidine or 70% isopropyl alcohol solution and avoiding contamination of the treatment area after cleansing the patient's skin. An injection approach should be used that reduces the number of skin piercings and uses the smallest gauge needle possible for injections. It is also important to avoid injecting into inflamed or infected skin, to avoid intraoral injections and to avoid injecting through previous layers of filler (Bailey et al., 2011; Ozturk et al., 2013; Cox and Adigun, 2011).

7. Herpes simplex infection

Reactivation of herpes simplex infection, especially when performing lip augmentation, is not an uncommon adverse effect and should be addressed properly. Patients with a history of recurrent herpes simplex outbreaks should receive prophylactic antiviral therapy in the form of valacyclovir 500 mg bid 2 days before the procedure and 3 days after. Patients with active lesions of herpes simplex infection should postpone their procedure. Patients who develop new lesions post injection need to be started on an appropriate antiviral regimen and appropriate oral antibiotic if a superadded bacterial infection develops (Funt and Pavicic, 2013; Sanchez-Carpintero et al., 2010).

8. Abscess and cellulitis

Bacterial inoculations can occur after filler injections as a result of skin surface breakage.(Daines and Williams, 2013) Inflammatory nodules that present with erythema, edema and tenderness, in other words, a "red angry bump", which presents within 3–14 days should be treated as an infection. The patient should be examined for fluctuance, and if fluctuance is noticed, incision and drainage are needed. Although staphylococci and streptococci bacteria are the most commonly identified organisms, the expressed material should be sent for broad culture for 10–21 days (under aerobic and anaerobic growth conditions). Another approach is to aspirate the lesion with an 18-gauge needle after applying topical anesthesia. The patient should be started on empiric broad-spectrum antibiotics immediately, selecting drugs that provide coverage against acid-fast bacilli, atypical mycobacteria, and MRSA, such as macrolide and tetracycline (clarithromycin 500 mg and minocycline 100 mg twice daily for 4–6 weeks). If there is no response after 48-h of follow up, take a 2 mm punch biopsy for tissue culture and adjust the antibiotics accordingly. Hyaluronidase can also be used to dissolve the nidus of the infection. In the case of severe infection, an immunocompromised patient, or infection in facial danger zones, hospitalization is warranted and intravenous antibiotics must be started (Funt and Pavicic, 2013; Narins et al., 2009; Levy and Emer, 2012; Sclafani and Fagien, 2009).

9. Mycobacteria

Post filler bacterial infection with *Mycobacterium abscessus* was reported in New York City in 2002 after a non-FDA approved HA filler was used (Hyacell) which was illegally imported from South America (Rousso and Pitman, 2010; Cohen, 2008). Rodriguez et al. (2013) reported three cases of Mycobacterium chelonae infection after a dermal filler injection that was isolated from clinic tap water (Rodriguez et al., 2013).

10. Biofilms

A biofilm is a collection of bacteria surrounded by a protective and adhesive matrix, which was first discovered on dental plaques (DeLorenzi, 2013; Kunjur and Witherow, 2013). Biofilms use the implanted filler as a surface on which to attach and excrete their own matrix. This matrix gives them the ability to survive, develop and resist antibiotic treatment up to a thousand times more effectively than planktonic bacteria. This excreted polymeric material entraps leukocytes and prevents phagocytosis (Cassuto and Sundaram, 2013; Marusza et al., 2012).

These microorganisms develop DNA mutations and achieve subsequent diversity (Narins et al., 2009). These bacterial colonies become active when conditions are favorable, for instance after trauma and manipulation. They can cause a variety of clinical presentations including cellulitis, abscesses, nodules or granulomatous inflammation, which can manifest weeks, months or even years after dermal filler injections (Cassuto and Sundaram, 2013).

The current mechanisms for culture have not successfully identified the causative bacteria. Diagnosis can be confirmed using PCR of bacterial protein or fluorescence in situ hybridization (Cassuto et al., 2009). Empiric antibiotics should be started while waiting for the PCR results; two or three antibiotic therapies would be appropriate, and macrolide and quinolone have been recommended, with clarithromycin 500 mg bid and ciprofloxacin 500 mg bid for 4–6 weeks (Funt and Pavicic, 2013; Constantine et al., 2014). Hyaluronidase can help cleave and fragment the enclosing matrix, hence reducing the amount of biofilm and helping the antibiotics work (Ozturk et al., 2013).

11. Foreign body granuloma

Foreign body granuloma is a chronic inflammatory reaction that entraps a foreign body, preventing its

migration. This reaction occurs because of the inability of the immune system to enzymatically degrade or phagocytose the foreign body (Funt and Pavicic, 2013).

The pathogenesis of these granulomatous responses remains unknown. HA fillers may still contain little amounts of protein contaminants after purification, which can carry a risk for hypersensitivity reactions and granuloma formations. On the other hand, cross-linking stabilizes HA filler and prevents its degradation, as cross-linking is breaking down, the components used to stabilize the HA filler may induce an immunologic reaction (Mamelak et al., 2009; Alsaad et al., 2012). The incidence of foreign body granuloma after the injection of HA fillers ranges from 0.02% to 0.4% (Lemperle et al., 2009; Lee and Kim, 2015).

Granulomatous reactions generally have a delayed onset after filler injections, appearing as red papules, plaques or nodules with a firm consistency which may result from fibrosis in late stages; if fluctuance is present, an infectious etiology must be ruled out (Lemperle et al., 2009). True granuloma must be confirmed histologically, by the presence of multinucleated giant cells that surround the basophilic product (Daines and Williams, 2013).

Intralesional hyaluronidase is an effective therapy for granulomatous lesions secondary to HA filler (Brody, 2005; Rzany et al., 2009; Curi et al., 2015). Alsaad et al. reported a case series of three patients who developed granulomatous reaction to HA filler three moths post procedure. All patients were injected with Prevelle Silk for periocular and perioral rhytides. Hyaluronidase was injected into the granulomatous nodules with a complete resolution of the skin lesions (Alsaad et al., 2012). Other treatments that can be used to resolve granulomas include systematic and intralesional corticosteroids, systemic oral antibiotics, intralesional5-fluorouracil and laser treatment (Cox and Adigun, 2011; Funt and Pavicic, 2013; Curi et al., 2015; Lemperle and Gauthier-Hazan, 2009; Park et al., 2011).

12. Vascular occlusion

Vascular occlusion is the most concerning complication regarding filler injections. It can be a localized occlusion, resulting in skin necrosis, or a distant occlusion causing blindness or cerebral ischemic events (Carle et al., 2015; DeLorenzi, 2014). Localized vascular occlusion results from either direct intravascular injection or the compression of the vessels by the injected filler material (Cox and Adigun, 2011).

Arterial occlusion due to intra-arterial injection usually presents with an immediate or early skin blanching and varying degrees of pain; if not treated swiftly, the affected skin will develop reticulated erythema, purpura and ulceration and consequently, scarring (Gilbert et al., 2012). Delayed onset arterial occlusion secondary to external compression by the injected filler can also occur (Hirsch et al., 2007).

Venous occlusion occurs either by accidental intravenous injection or by placing a large amount of the filler material in a small area leading to venous compression (DeLorenzi, 2014; Kassir et al., 2011). It has a more delayed presentation with persistent, dull aching pain, swelling and violaceous reticulated erythema of the skin (Sclafani and Fagien, 2009). These features can be misinterpreted as injection induced bruising, pain and swelling, but the severity and the persistence of the pain should alert the physician to the possibility of vascular occlusion (Gilbert et al., 2012).

Blindness is the most feared complication of fillers injection. It has been proposed that accidental high injection pressure of the supratrochlear, supraorbital, angular and dorsal nasal arteries which are branches of the external carotid artery will result in a retrograde flow of the filler emboli into the ophthalmic artery (Carle et al., 2015). Once the physician stops the pressure on the plunger, the arterial pressure will push the filler emboli into the retinal circulation resulting in the loss of vision (Carruthers et al., 2014). If the physician applies a greater force for a long time, the filler emboli can reach the internal carotid artery and then be propelled into the intracranial circulation resulting in cerebral ischemic events (Carle et al., 2015; Kim et al., 2014).

The main high risk facial zones for skin necrosis and embolization are the glabella, nasal ala and dorsum of the nose (Bray et al., 2010). Several measures can be taken to minimize the risk of vascular complications including: through understanding of the facial anatomy, aspiration before each injection, low pressure injections of minimal volumes (<0.1 ml/injection), dilution of the filler with lidocaine and/or epinephrine, keeping the needle moving (bolus injections should be given only in the periosteum plane), avoid injections in areas of previous scarring and use of blunt cannulas, which may reduce the risk of intravascular placement of the filler material (Funt and Pavicic, 2013; Levy and Emer, 2012; Cohen, 2008; DeLorenzi, 2014; Glaich et al., 2006).

If features of tissue necrosis appear, the injection should be stopped, and an immediate injection of hyaluronidase enzyme is crucial in order to minimize the amount of tissue necrosis (Beer et al., 2012). This enzyme acts by hydrolyzing HA by splitting the glucosaminidic bond between C1 of the glucosamine moiety and C4 of the glucuronic acid (Kassir et al., 2011). Several formulations of hyaluronidase can be used which include amphadase (derived from bovine testicular hyaluronidase), vitrase (derived from ovine hyaluronidase) and hylenex (a recombinant human hyaluronidase) (Rzany et al., 2009).

Although rarely done in clinical practice, especially in urgent situations such as impending tissue necrosis, preliminary skin testing is recommended for vitrase and amphadase because of their animal origin (Gilbert et al., 2012). Inject a significant amount of hyaluronidase (200 units) which can be diluted either with lidocaine to induce vasodilatation and HA dispersion or with saline to allow coverage

of a larger area. If there is no clinical improvement after 60 min, an extra volume of hyaluronidase can be injected again (repeat up to 4 cycles) (Cohen et al., 2015).

The adverse events of hyaluronidase are uncommon, with injection related side effects being the most commonly reported (Hirsch et al., 2007). Less than 0.1% of patients injected with hyaluronidase develop urticaria and angioedema but there are no reported cases of anaphylaxis after subepidermal injections (Lee et al., 2010). Be cautious when using hyaluronidase in patients with a history of bee allergy because hyaluronidase is considered to be one of the active components in bee venom (Gilbert et al., 2012).

Moreover, the application of warm compresses (for 5–10 min every 1–2 h) and vigorous massage are important to stimulate vasodilatation and disburse the bulk of the filler material respectively (Sclafani and Fagien, 2009; Beer et al., 2012). Additionally, apply a half inch of 2% nitroglycerin paste daily to the affected area to stimulate further vasodilatation (Dayan et al., 2011). Start the patient on 2 pills of 325 mg of aspirin daily for a week to prevent the further clot formation in association with antacid to avoid gastritis (Hirsch et al., 2007).

The patient should be followed up daily for clinical improvement or worsening. If the condition worsens, hyaluronidase, aspirin and NTG paste must be repeated daily for additional two to three days (Cohen et al., 2015).

If necrosis is progressive and not responsive to the above treatments, consider hyperbaric oxygen therapy (Dayan, 2013). Of note, topical oxygen therapy, low molecular weight heparin, systemic steroids, sildenafil, platelet-rich plasma filler removal through puncture and intravenous prostaglandin are reported to be of beneficial (Daines and Williams, 2013; Kim et al., 2014; Kang et al., 2015; Beleznay et al., 2014).

Proper wound care is important in order to minimize the risk of scarring.

In the case of vision loss or ocular pain, stop injection immediately and contact an ophthalmologist or an oculoplastic surgeon for urgent retrobulbar injection of hyaluronidase which can dissolve intravascular as well as extravascular hyaluronic acid (Carruthers et al., 2014).

13. In conclusion

HA fillers are the predominantly used dermal fillers worldwide. Luckily, most complications associated with HA filler injection are mild and self-limiting. The rare vascular and infectious complications associated with HA filler injection can be minimized with a thorough understanding of facial vascular anatomy, proper injection techniques and meticulous skin preparation. Early identification and a prompt intervention can significantly decrease the risk of long-term sequelae.

Conflict of interest

None.

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