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Treatment of Nasolabial Folds With Fillers

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Abstract

Background: Nasolabial folds are natural facial contours that can become more prominent with age, projecting a fatigued or drawn appearance. Reduction of the nasolabial folds is one of the most commonly performed dermal filler treatments. The three classes of dermal fillers currently in use are: Absorbable products, slowly absorbable products and non-absorbable products. Hyaluronic acid products are the most widely used dermal fillers in Europe and USA. Complications associated with temporary or biodegradable fillers are usually mild and transient and they most commonly present as erythema and swelling as a result of traumatic injection, or as asymmetry caused by inappropriate placement of the filler. Fillers are now the second most common minimally invasive procedure performed among dermatologists, behind botulinum toxin injections. Dermal fillers are an aesthetic treatment and patients should be made aware of the complications that can arise from their use. Simple preventive steps such as an aseptic technique, use of smaller gauge needles and hyaluronic acid, avoiding make-up, and use of prophylactic antibiotics help to reduce the incidence of side-effects.

Nasolabial folds are natural facial contours that can become more prominent with age, projecting a fatigued or drawn appearance. Reduction of the nasolabial folds is one of the most commonly performed dermal filler treatments[**1**, **2**, **3**, **4**, **5**].

Anatomy

Nasolabial/melolabial folds, course diagonally in the midface from the nasal ala toward the corner of the lip. Many factors contribute to nasolabial fold formation including soft tissue volume loss and dermal atrophy, reduced skin elasticity, descent of malar fat pads, and hyperdynamic midface musculature. The lateral nasal artery is the main vascular supply for the nasal tip and ala. It is in close proximity to the nasolabial fold, 2–3 mm superior to the alar groove [**6**, **7**, **8**, **9** ,**10**].

Patients Assessment

Patients with mild, moderate, and severe static nasolabial folds are candidates for dermal filler treatments (**Figure 1**). Patients presenting with excess laxity and hanging skin folds usually require surgical or thread interventionsv for significant improvement (**Figure 2**). Methods of wrinkle management can be divided into two basic categories: [**1**] Filler materials-intradermal (e.g., collagen) and subdermal (e.g., SoftForm); [**2**]

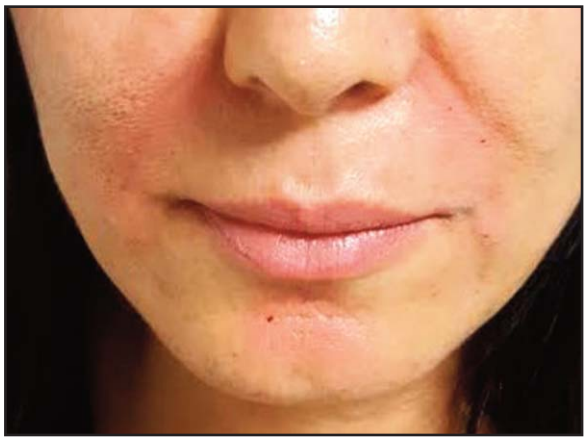

Figure 1. Nasolabial folds before treatment

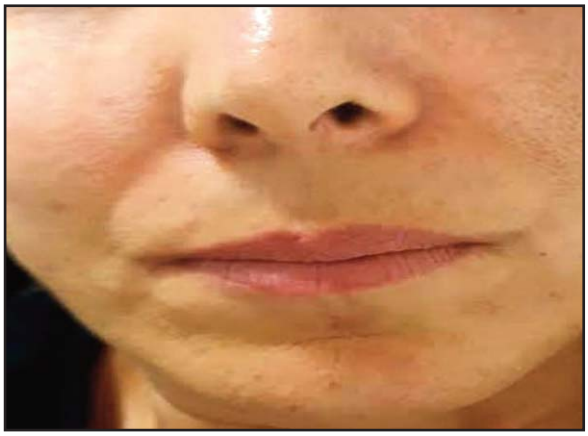

Figure 2. Nasolabial folds after 1 ml HA treatment

neuromuscular agents (e.g., Botulinum toxins) [**10**, **11**, **12**, **13**, **14**, **15**].

In aesthetic dermatology, the three classes of dermal fillers currently in use are:

1.Absorbable products (temporary; 3–6 months; e.g, hyaluronic acid (HA) and collagen fillers).

2.Slowly absorbable products (temporary; 6–24 months; e.g, HA, calcium hydroxyapatite and L-polylactic acid).

3.Nonabsorbable products (permanent;>24 months; e.g, polymethyl methacrylate and silicone) [**15**, **16**, **17**, **18**, **19**, **20**].

Dermal Fillers

HA based fillers appear to be ideal due to their low immunogenic potential and relatively long-lasting effect. HA products are the most widely used dermal fillers in Europe and USA. Collagen fillers, calcium hydroxylapatite fillers (Radiesse), Poly-L-Lactic acid (Sculptra), Polymethylmethacrylatea and Liquid Silicone fillers have been also used. HA is a naturally occurring glycosaminoglycan which exhibits no species or tissue specificity and is an essential component of the extracellular matrix in adult tissue. In the skin, it is located among the collagen fibers and has a hydrophilic capability, playing a critical role in the maintenance and regulation of hydration within tissues and contributing to skin turgor. This filler type consists of biphasic (particulate) and monophasic fillers (gel only). Approximately 50% of the total HA in the human body is found in the skin. Favorable physical properties of administered HA include ease of administration, resistance to deformation after application, acceptable persistence, biocompatibility, and reversibility with hyaluronidase. Hyaluronic acid, which is chemically identical across all species, is a ubiquitous component of mammalian connective tissue, where it forms the elastoviscous, hydrating, lubricating, and stabilizing matrix. Hyaluronic acid is also a normal component of human skin, where it provides a low degree of immunogenicity. The hydrophilic nature of HA allows it to maintain its shape using the body's own moisture. One gram of HA can bind up to 6 L of water. As a component of the extracellular matrix, intrinsic HA functions include space filling, lubrication, shock absorption, and protein exclusion. Over time, the injected hyaluronic gel is slowly absorbed by the surrounding tissues and disappears by a process called isovolumetric degradation [**3**]. Some authors beleived that the properties of mannitol could make HA fillers more suitable for rejuvenation. Mannitol could be expected to increase the durability of HA without foreign body reaction, and make injections easier. *Boulle* et al indicated the metabolism of 1,4-butenediol diglycidyl ether-crosslinked hyaluronic acid dermal fillers as acceptable persistence [**11**].

Hyun et al indicated the efficacy and safety of injection with poly-L-lactic acid compared with hyaluronic acid for correction of nasolabial fold. PLA is a biodegradable and bioabsorbable aliphatic polyester produced by carbonhydrate fermentation of corn dextrose, and was fisrt synthesized by French chemists in 1952. Each PLA molecule is relatively heavy (140 kDa). 2-50 μm in size and irregularly crystalline-shaped, all of which contribute to its slow physiological absorbtion. The half-life of L-polylactides is estimated at 31 days, with total absorption occuring by 18 months. PLA has been used for years in resorbable surgical materials such as sutures, plates and screws and in membranes for guided tissue regeneration in periodontal surgery. The efficacy and safety of lidocaine-containing monophasic hyaluronic acid filler has been observed. American Society for Aesthetic Plastic Surgery indicate that >85% of dermal filler procedures are now performed using HA derivatives [**21**,**22**].

Dextran is a complex with branched glucan and is generally used as a substrate of chromatography columns (Sehpadex) fort he seperation of proteins and a wound-cleaning agent (Debrisan). In urology, it has been used as a bulking agent fort he endoscopic treatment of vesicouretral refluc and urinary incontinence. The main component of the filler used aren composed off cross-linked dextran molecules with a positive surface charge. When injected subcutaneously, cross-linked dextran could directly increase in volume, and it is completely degraded in the vital tissue within 1 to 2 years. In addition, dextran microspheres are known to have a neocollagenesis effect. Through its collagen-forming ability, subcutaneously cross-linked dextran may offer long-lasting volume augmentation even after complete degradation. Cross-linked dextran is considered to be effective in soft tissue augmentations. *Shin* et al showed the efficacy and safety of a dextran filler in the treatment of nasolabial folds. *Lee* et al also studied this filler [**9**, **10**, **11**, **12**, **13**, **14**, **15**, **16**].

Moon et al did a comperative study of the effectiveness and safety of porcine and bovine atelocollagen in nasolabial fold correction. They thought bovine atelocollagen has disadvantages such as its potential patient hypersensitivity and possible immunological reaction, unlike human collagen that is made either by processing the collagen harvested from a cadaver donor or via laboratory culture of human fibroblasts. Despite this advantages, bovine atelocollagen is still widely used because it adverse reaction rate is low (%1.3) and can be easly predicted via pretreatment skin testing, and also because it can be easily obtained. However, issues regarding bovine spongiform encephalopathy (BSE) have recently been raised as researchers discovered that the histological structure of porcine-derived collagen is similar to that of human dermal collagen and that it does not have the risk of BSE10.

D' Aloiso et al indicated the efficacy and safety of cross-linked carboxymethylcellulose filler for rejuvenation of the lower face in a 6 months prospective open study16.

The Injection Technique

The injection technique is dependent on the filler, area to inject, and the physician and patient preference. To reduce injection and filling related pain, topical anesthetics or nerve blocks may be used. Some fillers contain lidocain to reduce injection pain. It is possible to use either a multiple puncture technique or a threading technique. The latter needs a lesser number of needle sticks. Filling can be performed retrograde or anterograde. Needle diameter is dependent on the choice of filler. For many HA fillers, 27-30 gauge needles are used. Some investigators prefer cannulas. The injections should be done with a slow motion to reduce pain, bruising, and risk of irregularities. Cold compresses before and after the procedure increase comfort and reduce swelling and tenderness. The treatment goal is the reduction of nasolabial folds without full effacement. Basic hyaluronic acid (HA) dermal filler products are recommended for treatment of nasolabial folds, such as Juvederm® Ultra XC, Juvederm® Ultra Plus XC or Restylane-L®, Xela® Revive or reshape, Stylage®. Mild nasolabial folds typically require a total volume of 0.8-mL HA, moderate nasolabial folds typically require a total volume of 1.6-mL HA and severe nasolabial folds typically require a total

volume of 2.4-mL HA. Most previous studies involving HA injection into the nasolabial folds show an average injection volume of 1.6 cc. But *Goodier* et al used and average of 0.58 cc HA. They observed that injection of a dermal filler, at low volumes, into either the nasolabial folds results in similar improvement to correction of the nasolabial folds. Local infiltration injection supplies including lidocaine hydrochloride 2% with epinephrine 1:100 000 buffered and 3-gauge, 1/2 –inch needle can be used for local anesthesia. Buffered 2% lidocaine-epinephrine solution can be used to achieve anesthesia for nasolabial folds. Both folds are anesthetized using six injections of 0.1 mL for a total volume of 0.6 mL. Topical benzocaine, lidocaine and tetracaine (BLT) may be used as an alternative for patients with high pain thresholds. For dermal filler injection, 30-gauge, ½-inch needle can be used. The use of dermal fillers is fully accepted into the nasolabial fold in male patients. However, the use of volumizers in the cheek is still a taboo. Both patients and injectors believe that cheek injections will lead to a feminine look. In an sssessment of female and male profile, the forehead indentation is very common due to projection of the supraorbital ridge in men. Nsal hump is also common in men, and the nasolabial angle should not be as open as in women. The anteromedial cheek is flatter in men and fuller in women. The chin is more projected and stronger in men [**1**, **2**, **3**, **4**, **5**].

For filler injection, serial puncture, linear threading, fanning, cross-hatching, tower technique and also perpendicular strut injection technique can be used. Nasolabial folds are generally treated with linear threading technique. In cases where a particular deep fold is present, layering the parallel lines is used to achieve the desired results. In order to effectively efface this area, the needle is placed medial to the fold. If placed within the deepest aspect of the fold or more laterally, there is a high likelihood of further deepening upon injection. The needle is typically inserted at the inferior border of the fold and advanced superiorly toward the alar facial junction. In many patients, the superior aspect of the fold required a layered injection because of more volume deficiency in this area [**3**].

Threading is a technique which involves depositing the product as the needle is withdrawn from the tissue. In this technique, the needle is inserted to its hub, taking care that the needle is in the very deepest portion of the dermis or in the subdermal tissues. If the skin dimples down with downward pressure on the needle, then the needle is in the dermis. If the needle can be visualized through the skin, then it is too superficial and will generally not produce an aesthetically pleasing effect. If there is little resistance to the needle and the product upon injection, then the needle is in the subcutaneous [**4**].

The fanning method is the preferred manner for achieving superior, natural appearing, and longer-lasting results. However, the amount of product that is used is dependent on the depth of the crease, the patient's desired outcome, and the patient's financial preferences. The fanning method is appropriate for placement of the product in the immediate subdermis or subcutaneous tissues. It is very difficult (if not impossible) to perform the fanning technique in heavily resistant dermal tissues. Because the subdermal tissues are less resistant, allowing for more diffusion, more product is usually needed for complete correction with fanning as compared with other techniques. In the fanning method, the needle is placed just below the dermis at a 30° angle with the bevel position irrelevant. The needle is passed back and forth under the fold, extending approximately 2 mm lateral to 2 mm medial to the fold. The product is deposited both as the needle is inserted and withdrawn, filling in an approximately 4-mm wide band of product with the fold in the center. The product should be deposited slowly and steadily. Injecting HA at 0.3 mL/min or slower has been determined to result in less ecchymoses. In most patients, it will take at least 1 mL of filler per fold to achieve a satisfactory result. It is important to achieve complete correction but to stop at the desired cosmetically appealing endpoint and refrain from overcorrection. Results tend to improve over the next couple of weeks as

inflammation subsides and as the product "settles" into the fold [**15**].

An optimal injection technique depends on the filling agent, the area and target to be corrected, and preference of the surgeon. Intradermal injection is a basic approach to treat deep wrinkles; however, occasionally, unfavorable results are encountered, such as conspicuous ridging or beading on or adjacent to the target wrinkle and negligible effects on wrinkles. Deep wrinkles/grooves accompanied with ptosis of the soft tissue are often not fully corrected by a single procedure and may need to be treated by a combination of intradermal and subdermal injections [**2**].

Performing the Procedure: Clean and prepare the skin lateral to the nasolabial folds with alcohol. Inject buffered 2% lidocaine-epinephrine solution subcutaneously. Allow a few minutes for anesthesia. Use of an epinephrine-containing product has inherent risks and benefits. Although it may mask a complication because of its blanching effect, it also may decrease the chance of bruising by constricting the blood vessels [**3**].

Number of injections: There are two linear thread injections and one fanning injection per side. All injections are placed medial to the nasolabial folds. Injections start at the inferior most portion of the nasolabial fold and proceed superiorly toward the nose. Dermal filler is injected in the mid- to deep dermis for treatment of nasolabial folds. Position the patient is in a 60-degree reclined position. Prepare the nasolabial folds with alcohol. The provider is positioned on the same side as the nasolabial fold to be injected [**4**].

Attach a 30-gauge, ½-inch needle to the pre-filled HA- dermal filler syringe. Ensure that the needle is firmly affixed to the dermal filler syringe to prevent the needle popping off when plunger pressure is applied. Prime the needle by depressing the syringe plunger until a small amount of dermal filler extrudes from the needle tip. The first injection point is medial to the nasolabial fold at the inferior portion of the fold. Insert the needle at a 30-degree angle to the skin, directing it toward the ala, and advance to the needle hub. Apply firm and constant pressure on the syringe plunger, while gradually withdrawing the needle to inject a linear thread of filler in the mid- to deep dermis. The second injection point is approximately 1 cm superior to the first injection point and placed as above. The third injection point is 1 cm superior to the second injection point and the fanning technique is used. Insert the needle at a 30-degree angle to the skin and advance until the tip lies at the edge of the ala. Inject filler in a linear thread as described above. Without fully withdrawing the needle from the skin, redirect the needle inferiorly and medially using small angulations to ensure dermal filler placement is contiguous. Repeat until desired correction is achieved. Compress the treatment area with thumb on the skin and first finger intraorally to smooth any visible or palpable bumps of filler product. If bumps do not easily compress, the area may be moistened with water and stretched between the provider's fingers. Additional swelling and bruising commonly occur after compression and manipulation of filler product. Repeat the above injections for the contralateral side of the face [**5**].

Tips: Avoid placing filler product in the superficial dermis as this may result in an undesirable visible ridge of filler, which does not readily compress. Avoid treating lateral to the nasolabial folds as this can exacerbate the folds. Watch for tissue blanching of the nasal ala and other ischemic signs or symptoms. If ischemia occurs, manage it. Cold compresses before and after the procedure increase comfort and reduce swelling and tenderness [**21**, **22**, **23**].

Blunt cannula: The blunt cannula provided advantages in mitigation of pain and vascular embolims, with a degree of correction similar to needle. The addition of blunt cannulas to the clinical setting may be appropriate. Vascular occlusion arising from injections of dermal fillers by thin-walled needles has been known to lead to long-term complications including pain, scarring, redness, pigment changes, epidermal and dermal necrosis. The soft tissue filler calcium hydroxylapatite has shown comparability and in some cases superiority to hyaluronic acid in terms of efficacy, safety, durability and volumes. Unfortunately, while vascular occlusions can

be mitigated in HA applications through the use of hyaluronidase, at present there is no compound for mitigated complications from calcium hydorxylapatite. Given the absence of a hyaluronidase equivalent compound for calcium hydroxylapatite, the use of blunt cannulas can be a strategy to limit the risk of adverse vascular events and reduces pain levels arising from use of thin-walled needles. In addition, use of cannulas is also recommended to avoid arterial occlusion, one of the most severe complications reported from needle treatment with dermal soft tissue fillers. Several features of the cannulas likely help account for improved patient safety. Because the port for material insertion is on the side of the device-rather than at the tip-the dermal filler is deposited adjacent to vasculature, i.e., into tissue, rather than into vessels. In addition, the tip of the cannula is dull and rounded rather than sharp. With the likelihood of transecting vessels or inserting product into vasculature reduced due to its design and side-port delivery, the cannula may also reduce the trauma of bruising, swelling, pain and vascular compromise. Microcannulas with blunt tips for filler injections have recently been developed for use with dermal fillers. Their utility, ease of use, cosmetic outcomes, perceived pain, and satisfaction ratings amongst patients in terms of comfort and aesthetic outcomes when compared to sharp hypodermic needles has not previously been investigated. *Fulton* et al compared injections of filler with microcannulas versus hypodermic needles in terms of ease of use, amount of fillerrequired to achieve desired aesthetic outcome, perceived pain by patient, adverse events such as bleeding and bruising and to demonstrate the advantages of single-port injection technique with the blunt-tip microcannula. Ninety-five patients aged 30 to 76 years with a desire to augment facial, décolleté, and hand features were enrolled in the study. Subjects were recruited in a consecutive manner from patients interested in receiving dermal filleraugmentation. Each site was cleaned with alcohol before injection. Anesthesia was obtained with a topical anesthesia peel off mask of lidocaine/tetracaine. Cross-linked hyaluronic acid was injected into the mid-dermis. The microcannula or a hypodermic needle was inserted the entire length of the fold, depression or lip and the filler was injected in a linear retrograde fashion. The volume injected was variable, depending on the depth and the extent of the defect. The injecting physician assessed the ease of injection. Subjects used the Visual Analog Scale (0-10) for pain assessment. Clinical efficacy was assessed by the patients and the investigators immediately after injection, and at one and six months after injection using the Global Aesthetic Improvement Scale (GAIS) and digital photography. Overall, the Global Aesthetic Improvements Scale (GAIS) results were excellent (55%), moderate (35%), and somewhat improved (10%) one month after the procedure, decreasing to 23%, 44%, and 33%, respectively, at the six month evaluation. There was no significant differences in the GAIS score between the microcannula and the hypodermic needle. However, the Visual Analog Scale for pain assessment during the injections was quite different. The pain was described as 3 (mild) for injections with the microcannula, increasing to 6 (moderate) for injections with the hypodermic needle. Bruising and ecchymosis was more marked following use of the hypodermic needle. They concluded that using the blunt-tip microcannula as an alternative to the hypodermic needles had simplified filler injections and produced less bruising, echymosis, and pain with faster recovery [**24**].

Results: Reduction of nasolabial folds is immediately evident at the time of treatment. Figure shows a woman with moderate nasolabial folds before (A) and after (B) treatment with 1-mL HA dermal filler.

Duration of Effects and Subsequent Treatments

Visible correction of nasolabial folds typically lasts 9 months to 1 year after treatment. Subsequent treatment with dermal filler is recommended when the volume of dermal filler product is visibly diminished and nasolabial folds become more evident, prior to their pretreatment appearance [**10**,**11**].

Follow-ups and Management

Patients are assessed 4 weeks after treatment to evaluate for reduction of nasolabial folds. Common issues reported by patients during this time include the following: Early (0–14

days), late (14 days–1 year), or delayed (more than 1 year) [**3**].

Adverse Effects

Although soft-tissue fillers have a very favorable safety profile, adverse events can occur. Minimal and self-limited complications are relatively common and perhaps would be more appropriately termed adverse sequelae rather than true complications. Such events include ecchymosis, swelling, and erythema. More significant yet self-limited complications also have occurred, including overcorrection, irregularities, filler visibility, Tyndall effect, and granuloma formation. Complications of greater severity also have been reported, such as visual impairment, skin necrosis, and anaphylaxis [**25**, **26**, **27**, **28**, **29**, **30**, **31**, **32**, **33**].

Bruising

Excellent technique will decrease the risk of bruising. Vitamin E, ginseng, garlic, ginger, gingko can cause bruising. Echinacea have been reported to reduce bruising. The fanning technique which is favored by many practitioners has been reported to increase the likelihood of bleeding. Because injectables are a blind technique, even experienced individuals may pierce a small vessel and cause ecchymosis [**26**].

Hematoma

It is an uncommon occurrence, but it can result from the inadvertent laceration of small facial blood vessels. Because of the supratrochlear artery and anastomosing blood vessels in the glabellar region, there may be a higher risk for hematoma when injecting frown lines. Immediate hypersensitivity is rare, and has been associated with bovine collagen [**27**].

Anaphylaxis

It could occur secondary to preservatives. Although infection is rare, the trauma of injection could lead to an HSV infection and potential long term pigmentary changes or small punctuate scars [**2**].

Swelling

Transient swelling may occur simply because of the irritation of placing a foreign implant within the skin or because of an indelicate technique. This swelling may last from 24 to 72 hours. Similarly, temporary tenderness may occur because of the needle trauma or because of the physical imposition and subsequent volume displacement on the skin from an implant. Generally, both swelling and tenderness will more pronounced in the semipermanent fillers compared with the shorter-acting injectables. Delayed small bumps may occur. This complication can occur with any filler, but is more likely with implants that need to be injected at least in the mid dermis or deeper such as the hyaluronic acid gels, calcium hydroxylapatite or polyl-lactic acid. Their etiology is unclear. Most commonly, it again may be due to a portion of an injection which was too superficial. These papules may have a bluish tint known from the Tyndall effect of placing this foreign gel in a superficial plane. Although delayed hypersensitivity reactions can occur in implants with animal particles, it is exceedingly rare in those implants with nonanimal derivatives to cause hypersensitivity reactions. Initially, hyaluronic acid implants performed outside the United States seemed to have higher immunogenicity risks, but this was most likely due to higher protein contents as well as impurities, and currently purification techniques have virtually eliminated this complication [**26**].

Erythema

Skin discoloration, particularly erythema along the injection site has been documented both in the hyaluronic acids and in calcium hydroxylapatite. Although it is unlikely to be a hypersensitivity reaction, there may be mast cell release contributing to this discoloration. Fortunately, in the vast majority of patients, the erythema will resolve in 2 to 3 days [**27**].

Itching and Tenderness

This postinjection “ache” most likely occurs due to volume displacement of the stretching of cutaneous nerves. Early complications can be as high as 80%, fundamentally transient

and subside with w long-lasting effects. Lumpiness may resolve with massage. However, with semi-permanent fillers injected too superficially, the lumpiness may remain for several months [**3**].

Foreign-body Reactions

Fine needle aspiration can be done for diagnosis [**32**].

Persistent Nasolabial Folds

Patients should be assessed for the following:

1.Static nasolabial folds: Additional dermal filler may be necessary if a volume deficit persists. Typically, 0.4–0.8 mL HA will achieve the desired result.

2.Dynamic nasolabial folds: Combination treatment with botulinum toxin may be required to achieve optimal results in patients with deep dynamic nasolabial folds,

3.Combining Aesthetic Treatments [**3**]

Complications associated with temporary or biodegradable fillers are usually mild and transient and they most commonly present as erythema and swelling as a result of traumatic injection, or as asymmetry caused by inappropriate placement of the filler. Temporary fillers can also cause late complications—for example, the Tyndall effect, a bluish discolouration, which occurs when hyaluronic acid is placed superficially in the skin. It is easily treated by injecting the enzyme hyaluronidase. Another rare complication reported with calcium hydroxylapatite and hyaluronic acid is necrosis, which is caused by intra-arterial injection of the filler [**30**].

Late Complications

Result from infections and hypersensitivity reactions to the materials, swelling, hyperpigmentation, and necrosis can be seen. Unlike the short-term complications, they are difficult to treat and cause more disfigurement and psychological damage. Tissue ischemia and tissue necrosis were evaluated a study. Of the 61 cases, the injection site most commonly associated with complications was the nose (32.8%; n = 20), followed by the glabella (26.2%; n = 16) and the nasolabial fold (NLF) (26.2%; n = 16). Hyaluronic acid was the most common filler implicated in necrotic complications, and collagen was the most common filler resulting in visual impairment. Consensus treatment of suspected intravascular injection includes immediate cessation of the injection, massage, warm compresses, topical nitroglycerine paste, and hyaluronidase (regardless of filler type). Other suggestions (but without proven efficacy) include removal of filler via puncture, systemic or topical steroids aspirin, low-molecular- weight heparin, and intravenous prostaglandins. An algorithm for the treatment of suspected intravascular injection is presented in Figure. Although HA fillers are considered immunologically inert, there are some studies that demonstrated delayed-onset nodule formation following the usage of HA fillers. The reported symptoms include lumps, sterile abscess and firm nodules. The reported incidence of these reactions was very low (0.5–0.8%) and the range of time to resolve these reactions was 1–52 weeks. But the true incidence of this complication is unknown because of underreporting by clinicians Given that 42 % of those who had experienced it admitted to more than one intravascular episode, it may reasonably be assumed that the incidence of skin necrosis as a sequela to intravascular injection is even less than that reported here.The symptom most often associated with intravascular injection was immediate pain upon administration of the product. Other acute symptoms included blanching, duskiness, and ecchymosis. In several cases, no signs were noted at the time of injection, and delayed compression of vessels by product was proposed as a possible mechanism of injury. The affected sites showed additional signs of vascular compromise within 1 to 2 days, including erythema, white or violaceous discoloration, edema, bruising, and ongoing pain. In a study, the signs that were most frequently suggestive of intravascular injection were minor livedo or mottled vascular change (in almost two-thirds of cases), followed by pallor, pain, pustules, and tenderness with edness. Unfortunately, avoiding vessels is difficult because the vascular supply of the face is rich, and smaller arterial vessels can be found wherever

injections are placed. In patients with "impending necrosis," the symptoms and signs improved, sometimes associated with early intervention, and resolved without sequelae. When soft-tissue loss occurred, slough, ulceration, and eschar developed within 3 to 7 days after injection [**30**, **31**, **32**, **33**].

Prevention Strategies

* Aspiration (although a negative or positive aspiration cannot be relied upon slow low-pressure injection technique;

* Continually moving the needle or cannula while injecting;

* Care during injecting while patients are under any form of anesthesia;

* Injecting small amounts at a time;

* Observing skin changes during injection and in the immediate postinjection period (for pallor, mottling), and taking adequate notice of the underlying anatomy [**2**].

The nasolabial fold and nose were the most common points at which intravascular injection occurred, followed by the forehead and glabella, and then the lower lip. However, risk reduction strategies should be applied universally because of the variability of human facial vascular anatomy. Also of concern was the finding that intravascular injection still occurred with 25 and 23 gauge cannulae (albeit less commonly), despite the assumption that cannulae present less risk than needles, however, it is postulated that cannulae may enter vessels at more fixed areas like branch points [**5**].

A variety of treatments were used, including hyaluronidase (in most cases at least 300–1500 IU, dependent on area of involvement and severity of incident as soon as the diagnosis is made and repeated hourly or as needed). Nitroglycerin paste, warm compresses, intravenous prostaglandins, topical and oral antibiotics, topical and oral corticosteroids, anticoagulant such as aspirin and low-molecular-weight heparin, topical oxygen infusion cream, massage, hydrocolloid dressings, and eventual surgical treatment. Adipose-derived stem cells were used in 2 cases of nasal tip necrosis. Because rare cases of intra-arterial embolization have been reported, clinicians should consider the use of blood thinners and vasodilators (e.g., ASA, NSAIDs, pentoxifylline, low-molecular weight heparin, alprostadil, sildenafil, tadalafil) to prevent thrombosis and embolization. Once necrosis has occurred, patients should be followed closely and diligent wound care should be implemented with petrolatum ointment or hydrocolloid dressings. Surgical revision of scars and laser therapy may be considered in 3 months (at the earliest) after resolution of the eschar. Intralesional triamcinolone may be considered in select cases. Sun avoidance is of utmost important to avoid the development of postinflammatory hyperpigmentation. Laser therapy with the PDL and fractionated 1,550 nm erbium laser may be incorporated to treat residual redness and textural changes. HBOT has been shown to increase collagen synthesis, angiogenesis, and generation of scavengers to destroy oxygen radicals. (14-30 day) [**25**, **26**, **27**, **28, 29**, **30**].

When using hyaluronidase, the range of doses applied was quite large (less than 20 U to more than 500 U), but the use by the majority of injectors of higher doses was in line with recently published recommendations to use large amounts of hyaluronidase (at least 200 U) to flood areas of potential necrosis with sufficient enzyme to break up or dissolve the filler as quickly as possible (recommend 15 to 20 units of hyaluronidase injected for every 0.1 mL of HA in areas of filler excess and can be used several times) (theoretical reduction in proinflammatory cytokines and growth factors mitigated by hyaluronidase). The majority of those who reported skin changes responded that they healed without sequela, only 7 % displayed moderate scarring that required surface treatments alone, and no patients required reconstructive surgery for severe scarring [**25**].

Hyaluronic acid is widely injected for nose and nasolabial fold augmentations. The vascular complications associated with these procedures include rare (<0.1 percent) soft-tissue necrosis and vision impairment, possibly caused by accidental intravascular filler injection and/or extravascular filler compression. Tissue ischemia resulting from intravascular injection and occlusion of the angular artery may occur with nasolabial fold treat-

ments. Signs of vascular compromise and ischemia include a violaceous reticular pattern or white blanching, and may be painful or painless. These changes may be seen on the nose and/or nasolabial fold, and can present immediately, or be delayed. One case report identified ischemic changes 6 hours after dermal filler treatment. Ischemia is managed urgently as it can rapidly progress to tissue necrosis. Nose and nasolabial fold augmentations with HA fillers can lead impending basal skin necrosis, possibly caused by intravascular embolism and/or extravascular compression. The key for preventing the skin ischemia from progressing to necrosis is to identify and treat the ischemia as early as possible. Early (<2 days) combination treatment with hyaluronidase is associated with the full resolution of the complication. LED therapy has the capacity to upregulate collagen and procollagen synthesis in human fibroblast cultures. The mechanism of pneumatic needleless injectors is microtrauma. RF device disperses its energy to an intradermal level at the depth of the insulated needle. These treatments have good cosmetic outcomes for skin ischemia [**26**].

In long-term delayed complications such as granulomas and ulceration are characterized by the chronicity. Late complications result from infections and hypersensitivity reactions to the materials. Recurrent infection, swelling, abscesses, dysaesthesia and discharging sinus can be seen. Delayed complications are more common with permanent fillers. They can induce a foreign body response by the host tissue leading to their encapsulation, which may generate the formation of a granuloma. They present as red, tender nodules, scars, or suppurative abscesses at the site of the initial injection or at distant sites because of migration of the filler particles. Presentation often occurs 5 years after the initial injection. *Karim* et al. reported the proportion to be as high as one in every 192 patients they treated. A retrospective study on polyalkylimide showed complications of 4.8%. This is too high when the disfiguring complication of hardening of the capsule, migration, and recurrent abscesses are taken into account. Various theories have been hypothesized for the cause of delayed complications. Implantation of a large quantity of fillers, impurities in the filler agent, irregularities in the surface of the filler, and the impact of biofilms are some hypotheses. The idea that biofilms can cause delayed granulomas after injection of permanent filler is gaining more support. Biofilms are structured communities of micro-organisms that are encapsulated in a self-developed polymeric matrix that irreversibly adhere to a living or inert substance. They were first observed on dental plaque. Bacteria account for 95% of the biomass on biofilms, which are formed when free floating bacteria adhere to a surface and become sessile. Biofilms are heterogeneous structures made up of bacterial colonies, and extracellular matrix made up mainly of polysaccharides. Once established on implant materials such as fillers they are extremely difficult to remove as they respond to stimuli, grow, and maintain a homeostatic environment. A conventional immune response by the host is weakened by impaired immune system penetration of the biofilm as they are less conspicuous. This is compounded by an altered gene expression, which allows for a thousand-fold increase in antibiotic resistance. In addition, the extracellular matrix prevents macrophage phagocytosis Once established, biofilms continue as low-grade smoldering infections that are characterized by a low host response and high resistance to antibiotics. Manipulation, trauma, or injection of another substance in close proximity can activate them causing an infection that can present clinically as cellulitis or even as an abscess. Current techniques for culture fail to isolate the offending bacteria and a sample is usually misdiagnosed as a sterile abscess. However, they can be identified by polymerase chain reaction and pyrosequencing techniques that identify the bacterial DNA. Early recognition is the key. If the swelling is fluctuant then the pus should be drained and sent for culture and sensitivity tests. If it is not, or there is no growth then the recommendation is to start patients on antibiotics (a macrolide and quinolone). Macrolides have effectively been found to prevent the formation of a biofilm. If this fails high dose steroids (Triamcinolone 20–40mg/ml intralesional) injected into the lesion could be considered as they help to control the chronic inflammation associated with the lesions. Excision is the last step [**25**, **26**, **27**, **28**, **29**, **30**].

Iatrogenic Blindness/Cerebral Infarction

It is rare, but disastrous complications. There is anastomosis of the nasal area, consisting of dorsal nasal artery from the ophthalmic artery, angular artery, and lateral nasal artery from the facial artery. Injection into the nasolabial fold or nasal dorsum may accidentally break into the anastomosis, resulting in retrograde embolism. There were 12 cases of visual impairment resulting from filler embolism to the ophthalmic vasculature. The injected substances were HA, PMMA, injectable dermal matrix, collagen, PLLA, and CaHa. The glabella was the most common site yielding visual complications (50%; n = 6), followed by the nose (33.3%; n = 4), forehead (8.3%; n = 1), and periorbital region (8.3%; n = 1). In all 12 cases, the signs and symptoms of visual loss developed within minutes of the filler injection. Visual impairment was almost always accompanied by pain in the affected eye. Other immediate symptoms included diaphoresis, nausea, headache, ophthalmoplegia, and ptosis. In 4 cases, a violaceous reticular discoloration was evident several days after the injection, which was followed shortly by soft-tissue necrosis in the glabella and nose. One patient experienced ischemic stroke in addition to vision loss. Various treatment attempts were used, including diuretic agents, antiplatelet agents, systemic steroids, and aspirin. In 7 cases, no information on treatment was provided. Only 2 of the 12 patients (16.7%) had complete recovery of vision, and 1 (8.3%) had partial recovery. Six of the 12 cases (50%) resulted in permanent complete blindness. Suggestions to diminish the risk of retinal artery occlusion as below;

1-Pay attention to the anatomy of the vessels around the orbit.

2-Blunt cannula is preferred.

3-Local anesthesia with epinephrine promotes artery to constrict, thus reduce the risk of facial filler delivery.

4-Aspiration before injection. It could demonstrate intravascular placement of the needle.

5-Inject the material when the needle is pulled back, move slightly to deliver the filler at different points along a line.

6-Limit injected filler volume to less than 0.1 ml with each pass.

7-Inject as slow and gentle as possible to decrease the injection pressure.

8-Inject into the superficial layer of superficial musculaaponeurotic system (SMAS), do not inject deeper layer.

9-Avoiding shaping by pressing or pushing or pinching hard [**29**].

The underlying mechanism for visual impairment after facial injection is related to retrograde embolization from peripheral vessels into the ophthalmic arterial system. Intra-arterially injected material is displaced via a high injection pressure past the origin of the retinal artery, and when the plunger is released, it is propelled into this system. Even a very small amount of material can cause embolization of the retinal artery because it is an end artery with no physiologic anastomoses. The retina is also very sensitive to ischemia. Factors contributing to this phenomenon are high injection pressures, the distance between injection site and retinal circulation, and the amount of injected material. If symptoms of visual impairment occur, the goal is to reduce intraocular pressure and dislodge the embolus to improve perfusion of the retina and optic nerve. There is no single reliable treatment for iatrogenic retinal artery embolism. Recommended measures include immediate ophthalmologic consultation, ocular massage, timolol eye drops, diuretics, hemodilution (with hydroxyethyl starch), corticosteroids, calcium channel blockers, anticoagulation, and needle decompression of the anterior chamber. Other modalities that have been used after fat embolism to the retinal artery include carbon dioxide and oxygen therapy, thrombolysis with urokinase, and vasodilation.96 However, attempts to reverse retinal artery occlusion are often unsuccessful. It is unclear whether the recovery is due to timely initiation of therapy, transient embolism, or favorable location of infarct in the retina. Unfortunately, in cases of vision loss, the outcome is grave regardless of the treatment rendered [**33**].

Minimisation of Long-term Complications

Simple preventive steps such as an aseptic technique, use of smaller gauge needles, avoiding make-up, and use of prophylactic antibiotics help to reduce the incidence of infection and lower the risk of a biofilm forming. By contrast, injecting large volumes of filler, injecting into infected areas of the face (presence of active acne), or injecting a second permanent filler into an area that has previously been injected, should be avoided. Most important controllable factor for surgeons is the speed and pressure of injection. Fillers should be injected as slowly and gently as possible, so that there will be no sufficient amount of facial filler being propelled into the vessel. Filler should be injected slowly and the needle withdrawn using the least amount of pressure. Other precautions include aspiration before injection, delivery of material at different points, and injection of small volumes per pass. The use of small-caliber needles has been advocated by some since they slow the speed of injection. The use of blunt needles in high-risk regions such as the glabella, nose, and NLF is another means of reducing injury to vessels. Most surgeons prefer blunt cannulas with small-bore needles and smaller syringes because they slow the speed of injection, and less likely to puncture the vessels. Others argue that larger syringe has a greater cross-sectional area, therefore theoretically allow lower injection pressure. However, the surgeon's control is severely impaired by using larger syringe for fine injection of facial filler. In my opinion, the injection force and speed, the limited injected filler volume per pass are more important variables to control. Another precaution is the use of epinephrine-containing local anesthesia to reduce the size of vessels. The injection technique differs with blunt tips: there is less movement and less subcision and consequently less trauma. However, these cannulae are prone to bend with multiple passes, and some planes may be difficult to breach with the blunt tip, resulting in excess accumulation of the product [**26**].

Combining Aesthetic Treatments and Maximizing Results

1-Botulinum toxin: Some patients excessively contract the lip levator muscles during smiling resulting in deep nasolabial folds and a "gummy smile." In these patients, combining dermal filler treatment of the nasolabial fold with botulinum toxin treatment of the levator labii superioris alaeque nasi muscle can improve reduction of nasolabial folds. Dermal filler in adjacent areas. Patients requiring nasolabial fold treatment may also require treatment of the malar area. Restoring midface volume often reduces nasolabial folds, and it is advisable to perform malar augmentation first and reassess nasolabial folds afterwards [**2**].

2-Dermal filler layering. Although moderate to severe nasolabial folds can be treated with an HA dermal filler, using the techniques described in this chapter, improved outcomes can often be achieved by layering two types of dermal fillers. Layering is considered an advanced procedure, which consists of placing a dermal filler with more structural support in areas of deep dermal volume loss and overlaying it with a thinner, more malleable dermal filler to smooth superficial fine lines and wrinkles [**3**].

3-Carbon dioxide therapy: Subcutaneous carbon dioxide injections are often used esthetic medicine. CO2 therapy improves local parameters of circulation, reduced localized adiposities and can be used for the treatment of chronic wounds. Nisi et al used CO2 therapy and HA for cosmetic correction of the nasolabial folds [**34**].

4-Radiofrequency: *Choi* et al observed successfully combination of intradermal radiofrequency and HA filler for the treatment of nasolabial folds. Ko et al also observed that a new device incorporating RF treatment before HA filler injection could represent a biocompatible and long-lasting advance in skin rejuvenation. The correction of midface volume deficiency using HA filler and intradermal RF combination seems good [**35**, **36**, **37**, **38**].

Secret Tips

1. Add: Oral (6o mg/day) and topical %2 HA to increase the durability of HA.

2. Do: Subcision in special cases (incisionless subcuticular undermining), depression could be lifted by the releasing action of the procedure and the formation of fibrotic tissue in the normal course of wound healing. Lee and Sung did subcision using a spinal needle cannula and a thread for prominent nasolabial fold correction [**39**].

Pricing

Dermal filler fees are based on the type of filler used, size and number of syringes, the injector's skill, and vary according to community pricing in different geographic regions. Prices range from $75to $300 per syringe of 0.8-1 mL HA for treatment of nasolabial folds in Turkey.

Contraindications

HA must not be administered to patients with any acute or chronic skin disease or inflammation (such as pimples, rashes or hives) within or close to the area selected for correction. HA must not be administered to patients with bleeding disorders or in patients who are taking thrombolytic or anticoagulants [**2,3**].

Future Research

New areas of research are focused around the introduction of enzymes that can break down biofilms on contact, the use of antibiotic-coated fillers, and the use of laser to destroy biofilms. If the risk of formation is minimized, the risk of disfiguring complications will also be reduced. Nevertheless, when complications do occur they should be managed systemically. Hand fatigue can contribute to reduced accuracy in volume flow and delivery speed. Continuous-flow injection-assisted device can suitable alternative to manual injections. In 2009 FDA, in 2011 EU approved this device [**40**].

Conclusion

Since the introduction of collagen as a standard injectable material in the 1980s, a number of filler materials have been manufactured and approved by the FDA. All FDA efficacy testing of newer fillers has been based on the collagen prototype, using split-face studies. New fillers merely had to meet or exceed the safety and efficacy standards of collagen products when collagen was injected into 1 NLF and the filler tested in the contralateral fold. Direct comparisons were then made between the duration of softtissue correction and the complications that occurred. Since 2010, collagen filler products have not been available in the United States, with the exception of bovine collagen, used as a carrier for PMMA microspheres. The FDA has approved a variety of different filler materials, each with a distinct composition, injection profile, and duration of effect. Many of them are in use off-label at the discretion of the physician. Currently, HA is the most commonly used injectable, followed by CaHa and PLLA.Therefore, it is not surprising that HA products are implicated most frequently in severe complications. These fillers also have different mechanisms of action and different periods of persistence in tissue. Among the temporary materials, HA remains in the tissue for 4 to 12 months, whereas collagen typically lasts only 2 to 4 months. Recent studies have shown that reinjection 4 to 5 months following initial treatment significantly increases the efficacy of HA products. CaHa and PLLA are considered semipermanent fillers and may last 1 to 2 years in tissue. The only FDA-approved permanent filler is PMMA. Although the collagen carrier of this filler resorbs over time, the microspheres do not degrade, resorb, or dissolve, yielding permanent correction of wrinkles. Even though soft-tissue fillers are generally safe, undesirable effects can occur with any type of filler. Adverse effects may result from injection techniques (eg, overcorrection, irregularities, Tyndall effect, intravascular injection) or can be host-initiated local events. Some of these effects may resolve with time, but others will require intervention based on severity and/or the type of filler used. Visual impairment, soft-tissue necrosis, permanent scarring, and

anaphylaxis are rare but severe events. *Hanke* et al published data pertaining to a 7-year period (1982-1989) and reported an average annual incidence of 0.09% for necrosis and abscess after collagen treatments. In 2002, based on a review of manufacturer-supplied data, *Friedman* et al. 24 examined the safety profile of HA injections performed outside the United States. The overall incidence of AE was reportedly 0.15% in 1999 and 0.06% in 2000. *Narins* et al. 32 used information from spontaneous drug AE reporting (SAER) systems to identify the more severe HA-related complications and reviewed the published cases in the United States in 2004. They estimated the incidence to be less than 0.001%. Generally, "lighter" products such as the human collagens and the medium hyaluronic acids such as Restylane and Juvederm Ultra are very appropriate for the lips, marionette lines, nasolabial folds, fine rhytides, glabelar folds, the periorbital and for filling acne scars. The "heavier" injectables such as calcium hydroxylapatite, cross linked hyaluronic acid (Perlane, Medicis, Scottsdale, AZ), and fat are excellent for the nasolabial folds, marionette lines, prejowl sulcus cheeks, the temporal fossa and scars. Fillers are now the second most common minimally invasive procedure performed among dermatologists, behind botulinum toxin injections. Dermal fillers are an aesthetic treatment and patients should be made aware of the complications that can arise from their use [**41**].

References

1. Dayan SH, Bassichis BA.Facial dermal fillers: selection of appropriate products and techniques.Aesthet Surg J 2008; 28: 335-347. PMID: 19083546
2. França Wanick FB, Almeida Issa MC, Luiz RR, Soares Filho PJ, Olej B. Skin Remodeling Using Hyaluronic Acid Filler Injections in Photo-Aged Faces. Dermatol Surg 2016; 42: 352–359. PMID: 26918965
3. Noh TK, Moon HR, Yu JS, et al. Effects of highly concentrated hyaluronic acid filler on nasolabial fold correction: A 24-month extension study. J Dermatolog Treat 2016: 27: 570-514. PMID: 27121901
4. Maio M. Ethnic and Gender Considerations in the Use of Facial Injectables: Male Patients. Plast. Reconstr. Surg 2015; 136: 40S-43S. PMID: 26441109
5. Wollina U. Perioral rejuvenation: restoration of attractiveness in aging females by minimally invasive pr ocedures. Clin Interv Aging 2013; 8: 1149-1155. PMID: 24039412
6 Iannitti T, Morales-Medina JC, Coacci A, Palmieri B. Experimental and Clinical Efficacy of Two Hyaluronic Acid-based Compounds of Different CrossLinkage and Composition in the Rejuvenation of the Skin. Pharm Res 2016; 33: 2879-2890.PMID: 24962508
7. Goodier M, Elm K, Wallander I, Zelickson B, Schram S. A randomized comparison ofthe efficacy of low volume deep placement cheek injection vs. mid to deep dermal nasolabial fold injection technique forthe correction of nasolabial folds. J Cosmet Dermatol 2014; 13: 91-98. PMID: 24910271
8. Shin SJ, Her Y, Yu DS, Kim CW, Kim SS. Twenty-four-week multicenter, evaluator-blinded clinical study of the efficacy and safety of a dextranfiller in the treatment of nasolabial folds. Dermatol Surg 2014; 40: 652-657. PMID: 24852469
9. Lee YB, Song EJ, Kim SS, Kim JW, Yu DS. Safety and efficacy of a novel injectable filler inthe treatment of nasolabial folds: polymethylmethacrylate a nd crosslinked dextran in hydroxypropyl methylcellulose. J Cosmet Laser Ther 2014; 16: 185-190. PMID: 24684547
10. Moon SH, Lee YJ, Rhie JW, et al. Comparative study of the effectiveness and safety of porcine and bovine atelocollagen in Asiannasolabial fold correction. J Plast Surg Hand Surg 2015; 49: 147-152. PMID: 25272190
11. Kim BW, Moon IJ, Yun WJ, Chung BY, Kim SD, Lee GY, Chang SE. A Randomized, Evaluator-Blinded, Split-Face Comparison Study of the Efficacy and Safety of a Novel Mannitol Containing Monophasic Hyaluronic Acid Dermal Filler for the Treatment of Moderate to Severe Nasolabial Folds. Ann Dermatol 2016; 28: 297-303. PMID: 27274627
12. Narurkar VA, Cohen JL, Dayan S, et al. AComprehensiveApproach toMultimodal Facial Aesthetic Treatment: Injection Techniques and Treatment Characteristics From the HARMONY Study. Dermatol Surg 2016; 42: 177–191. PMID: 27128246
13. Wu Y, Sun N, Xu Y, Liu H, Zhong S, Chen L, Li D. Clinical comparison between two hyaluronic acid-derived fillers in the treatment of nasolabial folds in Chinese subjects: BioHyalux versus Restylane Arch Dermatol Res 2016; 308: 145–151. PMID: 26924549
14. Joo HJ, Woo YJ, Kim JE, Kim BJ, Kang H. A Randomized Clinical Trial to Evaluate the Efficacy and Safety of Lidocaine-Containing Monophasic Hyaluronic Acid Filler for Nasolabial Folds. Plast Reconstr Surg 2016; 137: 799-808. PMID: 26910660
15. Mashiko T, Kinoshita K, Kanayama K, Feng J, Yoshimura K. Perpendicular Strut Injection of Hyaluronic Acid Filler for Deep Wrinkles Plast Reconstr Surg Glob Open 2015; 3: e567. PMID: 26893992
16. D'Aloiso MC, Senzolo M, Azzena B. Efficacy and Safety of Cross-Linked Carboxymethylcellulose Filler for Rejuvenation of the Lower Face: A 6-Month Prospective Open-Label Study. Dermatol Surg 2016; 42: 209–217. PMID: 26771686
17. Choi WJ, Han SW, Kim JE, Kim HW, Kim MB, Kang H. The Efficacy and Safety of Lidocaine-Containing Hyaluronic Acid Dermal Filler for Treatment of Nasolabial Folds: A Multicenter, Randomized Clinical Study. Aesthetic Plast Surg 2015; 39: 953–962. PMID: 26493557

18. Kopera D, Palatin M, Bartsch R, Bartsch K, O'Rourke M, Höller S, Baumgartner RR, Prinz M. An open label uncontrolled, multicenter study for the evaluation of the efficacy and safety of the dermalfiller Princess VOLUME in the treatment of nasolabial folds. Biomed Res Int 2015; 2015: 195328. PMID: 25821787

19. Leonardis M, Palange A. New generation filler based on cross-linked carboxymethylcellulose: study of 350 patients with 3-yearfollow-up. Clin Interv Aging 2015; 10: 147-155. PMID: 25609932

20. Galadari H, van Abel D, Al Nuami K, Al Faresi F, Galadari I. A randomized, prospective, blinded, splitf face, singlecenter study comparing polycaprolactone to hyaluronic acid for treatment of nasolabial fol d. J Cosmet Dermatol 2015; 14: 27-32. PMID: 25564797

21. Park KY, Ko EJ, Kim BJ, et al. A multicenter, randomized, doubleblind clinical study to evaluate the efficacy an d safety of PP-501 B in correction of nasolabial folds. Dermatol Surg 2015; 41: 113-120. PMID: 25521103

22. Hyun MY, Lee Y, No YA, et al, Efficacy and safety of injection with poly-L lactic acid compared with hyaluronic acid for correction of nasolabial fold: a randomized, evaluator-blinded, comparative study. Clin Exp Dermatol 2015; 4: 129-35. PMID: 25319932

23. Lee JH, Choi YS, Kim SM, et al. Efficacy and safety of porcine collagen filler for nasolabial fold correction in Asians:a prospectivemulticenter, 12 months fo llow-up study. J Korean Med Sci 2014; 29: S217-221. PMID: 25473212

24. Beer KR. Safety and effectiveness of injection of calcium hydroxylapatite via blunt cannula compared to i njectionby needle for correction of nasolabial folds. J Cosmet Dermatol 2014; 13: 288-296. PMID: 25399621

25. Darling MD, Peterson JD, Fabi SG. Impending necrosis after injection of hyaluronic acid and calcium hydroxylapatite fillers: report of2 cases treated with hyperbaric oxygen therapy. Dermatol Surg 2014; 40: 1049-1052. PMID: 25077741

26. Gladstone HB, Cohen JL. Adverse effects when injecting facial fillers. Semin Cutan Med Surg 2007; 26: 34-39. PMID: 17349561

27. Kunjur J, Witherow H. Long term complications associated with permanent dermal fillers. Br J Oral Maxillofac Surg 2013; 51: 858-862. PMID: 23962591

28. Ozturk CN, Li Y, Tung R, Parker L, Piliang MP, Zins JE. Complications following injection of soft-tissue fillers.Aesthet Surg J 2013; 33: 862-877. PMID: 23825309

29. Beleznay K, Carruthers JD, Humphrey S, Jones D. Avoiding and Treating Blindness From Fillers: A Review of the World Literature Dermatol Surg 2015; 41: 1097–1117. PMID: 26356847

30. Manafi A, Barikbin B, Manafi A, Hamedi ZS, Moghadam S. Nasal Alar Necrosis Following Hyaluronic Acid Injection into Nasolabial Folds: A Case Report Word J Plast Surg 2015: 4: 74-78. PMID: 25606480

31. Sun ZS, Zhu GZ, Wang HB, et al. Clinical Outcomes of Impending Nasal Skin Necrosis Related to Nose and Nasolabial Fold Augmentation with Hyaluronic Acid Fillers. Plast Reconstr Surg 2015; 136: 434e. PMID: 26397262

32. Faria KM, Fonseca FP, Silva WG, et al. Fine needle aspiration cytology inthe diagnosis of perioral adverse reactions to cosmetic dermal fillers. Oral Surg Oral Med Oral Pathol Oral Radiol 2014; 117: e393-395. PMID: 24184060

33. Li X, Du L, Lu JJ. A Novel Hypothesis of Visual Loss Secondary to Cosmetic Facial Filler Injection. Ann Plast Surg 2015; 75: 258-260. PMID: 26207560

34. Nisi G, Cuomo R, Brandi C, Grimaldi L, Sisti A, D'Aniello C. Carbon dioxide therapy and hyaluronic acid for cosmetic correction of the nasolabial folds. J Cosmet Dermatol 2016; 15: 169-175. PMID: 26786710

35. Seok J, Choi SY, Park KY, et al. Depressed scar after filler injection successfully treated with pneumatic needleless injector and radiofrequency device. Dermatol Ther 2016; 29: 45-47. PMID: 26301992

36. Kim H, Park KY, Choi SY, et al. The efficacy, longevity, and safety of combined radiofrequency treatment and hyaluronic Acid filler for skin rejuvenation. Ann Dermatol 2014; 26: 447-456. PMID: 25143672

37. Ko EJ, Kim H, Park WS, Kim BJ. Correction of midface volume deficiency using hyaluronic acid filler an d intradermal radiofrequency. J Cosmet Laser Ther 2015; 17: 46-48. PMID: 25264587

38. Choi SY, Lee YH, Kim H, et al A combination trial of intradermal radiofreqency and hyaluronic acid filler fort he treatment of nasolabial fold wrinkles: a pilot study. J Cosmet Laser Ther 2014; 16: 37-42. PMID: 24131095

39. Lee SY, Sung KY. Subcision using a spinal needle cannula and a thread for prominent nasolabial fold correction. Arch Plast Surg 2013; 40: 256-258. PMID: 23730604

40. Lorenc ZP, Bruce S, Werschler WP. Safety and efficacy of a continuous-flow, injection assisted device in delivery of dermal fillers. Aesthet Surg J 2013; 33: 705-712. PMID: 23671210

41. Goodman GJ, Roberts S, Callan P. Experience and Management of Intravascular Injection with Facial Fillers: R esults ofa MultinationalSurvey of Experienced Injectors. Aesthetic Plast Surg 2016; 40: 549-555. PMID: 27286849