Does an ideal filler exist?

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Abstract

Introduction: Aesthetic procedures of skin regeneration and treatments are finding more and more use in daily practice. Today's trend leans towards non-invasive procedures compared to the number of these procedures performed in the previous years. The correct application of hyaluronic acid filler by trained doctors is accompanied by a small number or no complications at all. Purpose of this paper: To emphasize the importance of qualification in hyaluronic acid (Filler) injection procedures. To acknowledge and understand the possible complications and re-emphasize the ways of managing them after the application of hyaluronic acid. Materials and Methods: Patients treated with hyaluronic acid injections (Fillers) who developed complications after the procedure. The selected sample in this referral bases on the material and experience from our clinical cases encountered in the daily practice of 15 years. Results: Complications after hyaluronic acid injections are classified as immediate complications and delayed complications. The number of complications immediately after the procedure is larger compared to the number of complications that develop later and includes pain, edema, discomfort, hematoma, infections, nodules, vascular-necrosis compression, blindness. The number of delayed complications is smaller and includes infections, granulomas, filler migration. Conclusions: Every injection procedure (Filler) contains the possibility of

developing complications. Therefore, we can't say that an ideal filler does exist. Hyaluronic acid injection procedures are safe and effective procedures if applied by trained medical personnel. Having strong knowledge of anatomy and acquiring updated information on this sub-specialty, especially on the treatment of complications, is a necessity for the medical staff that performs these procedures. Aesthetic medicine is the bridge between medicine and art and should be entrusted to experts.

Introduction

Dermal fillers injections are among of the most performed procedures in the aesthetic dermatology practice. These procedures are increasing very fast during the last years. They are commonly known as tissue fillers, wrinkle fillers or injectable implants and are mostly used for filling of folds and replacement of soft tissue volume loss due to diseases or skin ageing. (1) Applying a dermal filler is generally well tolerated and safe, but occasionally they can develop complications. Of course, during the last years, the number of complications reported is increasing. Doctors must be aware for these complications that can be mild but medical emergency as a hypersensitive reaction. When performed by a medical doctor with deep knowledges of anatomy and good training the majority of these complication can be avoided. The recognition of early signs and symptoms prompts a correct treatment at early stages, avoiding the development of possible immediate or delayed complications.

Classification of dermal fillers

According to the literature, there are more than 160 filler products made from 50 different manufactures available worldwide. (2) The most common classification of dermal fillers is based on their longevity into temporary, semi-permanent and permanent fillers. According to one classification fillers are divided into biodegradable and nonbiodegradable (1, 2).

Biodegradable fillers – temporary or semi-permanent fillers (absorbable fillers)

Biodegradable fillers contain components of the derma (polysaccharide) that gradually degrade and are absorbed by the body (3). They fill the gaps between the wrinkles, increasing the hydration of the skin. These fillers are enzymatically degraded or desegregating from the mimic facial movements and absorbed. This process directly determines the duration of the treatment, diving them into temporary or semi-permanent, which also varies according to the patient's lifestyle (exposure to sunlight or solar tanning bed, smoking, drinking alcohol, stress) (4).

Some examples of biodegradable fillers are collagen, hyaluronic acid (HA, calcium

hydroxyapatite (CaHa) and poly-L-lactic acid (PLLA).

Collagen was the first injectable filler approved by the US Food and Drug Administration (FDA) (2). It makes up 70% to 80% of the dermis, which is gradually lost and becomes fragmented with age. It is less viscous and sometimes is more useful in the correction of fine lines and wrinkles because it is less likely to produce irregularities when injected superficially. The use of collagen is replaced with HA fillers.

HA is a polysaccharide with hydrophilic properties (a glycosaminoglycan disaccharide composed of an alternating and repeating unit of D-glucuronic acid and N-acetyl-D-glucosamine) which is a natural component of extracellular matrix (5). HA and its derivatives are considered to be the most popular dermal fillers due to their hydroscopic properties, biocompatibility, and reversibility.

Non-biodegradable fillers – permanent fillers. (non-absorbable fillers)

Nonbiodegradable fillers acts as foreign agents, which generate a reaction defined as chronic granulomatous reaction, that subsequently stimulates collagen deposition (3). Injected in the deep derma, they offer a longer effect that lasts about 2 years. Therefore, the patients do not require periodically refilling. However, they are prone to developing long-lasting complications that presents a challenge in their management. Some examples of nonbiodegradable fillers include polymethylmethacrylate (PMMA), polyalkylimide and silicone (1).

Complications

Even though dermal fillers that are used today are generally safe, complication can occur. They are commonly a result of 3 main actors:

(I) Medical Doctor (the injector and injection techniques)

(II) The product used as a dermal filler

(III) The patient itself (Table I).

Table I. *Factors that determine the occurrence of complications.*

Medical Doctor Strong knowledge on anatomy and technique Adequate training Adequate environment: good lighting, proper tools
Product A certified and approved filler The usage of right filler according to the indication
Patient Medical history and preexisting conditions Allergies, Active infections at the site, Inflammatory skin disorders, Neuromuscular disorders, Pregnancy and Lactation, Medication (anti-platelets and anticoagulants)

We have divided the complications of dermal fillers into three main categories: immediate, early and delayed, depending on the time of their appearance regarding the beginning of the procedure (Table II). Another way to divide these complications is temporarily and permanent complications. The larger part of possible side effects is mild and transient, but in the everyday practice and literature, cases of irreversible functional and aesthetic deficits have been reported (2).

Table II. *Filler complications regarding the time of onset.*

Immediate-onset Events (up to 14 sec post-procedure)
Injection site reactions: erythema, oedema, pain, ecchymosis (Allergy, Inflammation)
Early-onset Events (day to weeks post-procedure)
Infections
Type I Hypersensitivity reactions
Non-inflammatory nodules/ irregularities
Skin discoloration
Tyndall effect
Vascular occlusion/Emboli
Late-onset Events (weeks to years post procedure)
Malar oedema
Permanent discoloration
Type IV Hypersensitivity reactions
Infection (mycobacterial, biofilm related)
Inflammatory nodules and foreign body granulomas
Migration of filler material

Injection site reaction

Injection site reactions such as erythema, oedema, pain, discomfort, or ecchymosis usually have immediate onset, up to seconds after the procedure because of the local trauma. This side effects are mild, and they tend to persist for a short time, respectively erythema up to a few

hours and oedema up to a couple of days to a week (2). Their short longevity is explained with the superficial placement of the filler material (6). Pain is a common side effect; however, it can be minimized with several techniques such as using small needle gauge or topical anesthetic agents prior of the injection, cold ice compresses before and after the procedure and any NSAIDs immediately after. Bruising and ecchymosis is also considered a common complication. It is a result of extravasation of blood from the perforated dermal vessels or their rupture, either from the needle or the pressure caused from the filler material (7). Ecchymosis are commonly located in lower eyelids, upper third nasolabial fold, the upper lip, the lateral edge of the lower lip, and perioral rhytids and they appear immediately after the injection and gradually resolve within 5 to 10 days (7). Bruising can be either more present in a person that is using anticoagulant therapy and can be minimize if you can advise the patient to stop this medication a few days before the procedure, and the techniques low injections and using a blunt cannula can minimize this side effect. The other advice for your patient is to camouflage correctly and to use a medical make up to cover it perfectly during the first days. Erythema on the side of injection is usually mild and transit complication and can be minimize by applying a corticosteroid cream on the side for few days.

Adequate environment, a professional and good lighting during the procedure, a comfortable medical chair, an adequate necessary space are factors that influence in the possibility of happening some side effects during and after the filler procedure (Fig. 1)

Fig. 1. *Bruising and Hematoma.*

Injection

Different infections (viral, bacterial and fungal) are noticed after the filler injection procedure due to the fact that the skin barrier is disrupted and the aseptic rules during the procedure are not to the demand. However, under favourable circumstances such as lack of appropriate preparation of the skin and adequate precaution, they can occur as the skin surface integrity breaches. The most common pathogens include staphylococcus, streptococcus, mycobacteria, viruses, yeasts and polymicrobial species. This complication can be noticed either a day after

(Herpes simplex), few days after but either a long period after the injection.

Referring our experience and as documented in literature, Herpes simplex infections are more often complications and can be triggered by lip filler augmentation or treating the fine smokers' lines in upper lips area. Therefore, a prophylactic antiviral therapy should always be considered prior procedure in those patients with a history of recurrent Herpes simplex outbreaks (2). Oral acyclovir should be taken two or three days prior the procedure and 1 day after for prophylactic reason. In cases of reactivation take in consideration to treat it locally or orally depend in the severity. If a patient has an active lesion of Herpes simplex the day of the procedure never perform a filler injection. Other infections due to streptococcus or staphylococcus microorganism can lead to abscess formation and cellulitis. The treatment of these complications by oral antibiotics is a must and should be perform as soon as possible especially in the eyes cellulitis as an emergency in dermatology.

A delayed infection can be noticed due to Mycobacterium chelonae and mycobacterium abscesses especially if is injected a contaminated filler (19). To avoid this, it is necessary not just the aseptic measures of the field of injection but either to be careful or to choose a certified filler.

Biofilms are a bacterial community which is surrounded by a protective and adhesive matrix, made by their own excreted polymers. This gives them the ability to develop and survive, even against the treatment (13). During the puncture of the skin surface, biofilms that resides on the surface, can enter and cause a local infection, a systemic infection or a granulomatous reaction depending on the depth of their penetration (14). It is classified either as inflammatory nodules and the treatment alternatives are antibiotics and in some cases corticosteroids (Fig. 2).

Fig. 2. *Infection.*

Hypersensitivity reactions (immediate or late - onset inflammatory adverse reactions)

The risk of developing hypersensitivity reactions must also be taken into consideration in every injection procedure. It may be triggered by the implantation of fillers, by the volume of the product injected or by the poor placement of the filler material. The temporary dermal fillers such as HA are more biocompatible and do not usually cause hypersensitivity reactions. Depending on the time of hypersensitivity reactions onset, it can be classified as acute (occur within minutes or hours after injections) and delayed (typically occur 48-72 h after injection but may be seen even several weeks or months post injection and can persist for months) (8). When the reaction is immediate, it is mediated by immunoglobulin E, describing a Type I Hypersensitivity with the typical signs such as erythema, pruritus, edema and rarely even anaphylaxis. These cases respond well to systemic corticosteroids and antihistamine (2). Always take in consideration the possibility of hypersensitivity due to lidocaine if you inject a filler with lidocaine and ask the patient prior the procedure.

Type IV hypersensitivity reaction appears later in time. It is manifested with erythema and oedema and is considered a delayed complication mediated by T-lymphocytes. The etiology of delayed of hypersensitivity to HA fillers is not completely understood (20), but triggering factors may be found like infections, trauma, vaccines, and different properties of the filler. (20, 21) Most of the late-onset adverse reactions are immune-mediated or inflammatory in nature. Most of them seem to have an immunological nature, on a background of genetic predisposition. These cases do not respond to antihistamines and often it is needed the removal of the allergen (9). Another possible complication to be aware is the hypersensitivity during the injection of hyaluronidase during the filler removal procedure. In this case you have to start immediately systemic corticosteroids.

Granulomatous reactions and nodules are rare late onset adverse reaction to HA fillers and much more frequent with permanent fillers. (20) A foreign body granuloma is clinically manifested as a nodus at the site of injection and appear after a period of time as a late complication. Always this complication needs a biopsy to be confirmed (18). Delayed reactions to HA fillers are treatable with systemic corticosteroids and hyaluronidase in case of lumps (21).

Non-inflammatory and inflammatory nodules

Nodules are another non-rare filler complication. Clinically they are prescribed as a bulge at the site of injection. It can appear early, within hours and days after filler application or after months or years (delayed nodules as a delayed complication). Based on the etiology there are divided into two categories: inflammatory and noninflammatory nodules.

Noninflammatory nodules are painless, non- erythematous and evident shortly after procedure. They arise from incorrect techniques, such as superficial placement, excess filler usage or incorrect product for the indication. In some cases, it can result due to migration of the product (21). Management include local massage at the side of injection or if it doesn't work, hyaluronidase injection(150IU/ml) is a treatment of choice for HA-filler. Performing the correct technique followed by local massage in the early post-procedure stage can prevent

noninflammatory nodules. It is important to choose the correct filler product for the correct indication and area (Fig. 3).

Fig. 3. *Non inflammatory nodus*.

Inflammatory nodules are painful, erythematous, and tender. They are either a result of an infection (Biofilms) or foreign body granulomas. Foreign body granuloma is a chronic inflammatory reaction of the body, which occurs as the immune system is not able to degrade or phagocytose this foreign material (16). This leads to the formation of multinucleated giant cells, which are characteristics of granulomas. Granulomas usually develop late, after the dermal filler injection as a delayed complication. The possibility of developing granulomas depends on the material used (usually it is seen in non-biodegradable fillers), large, injected volumes of the filler, the high molecular weight of the filler injected, infection or traumas at the site of dermal filler injection. (2, 17, 18)

Management typically includes local corticosteroids injection with hyaluronidase to the nodules and if it doesn't work a biofilm should be suspected. In these cases, a broad-spectrum antibiotic (quinolones or macrolides) should be use for a minimum of 4 weeks. The excision and a biopsy of granuloma can be a treatment of choice.

Skin discoloration

Skin discoloration as a late complication is in the form of hyperpigmentation post-inflammation or post-ecchymosis that are generally seen in patients with Fitzpatrick skin type IV-VI. Changes in the pigment can also happen when the material is placed superficially or with overcorrection (8).

Tyndall effect

It is an immediate complication presented as a 'bluish discoloration' of the skin and looks similar to an ecchymosis. As an inappropriate injection technique Tyndall effect happens when the filler is placed superficially and can cause scattering of blue light waves or the deposition of hemosiderin from intradermal bleeding. (13, 23) This discoloration usually dissolves within a couple of days or can persist for long period. Can be managed if you use a hyaluronidase first and re inject a filler a day of few days later.

Vascular occlusion/emboli

Vascular compromise is a rare complication but the most concerning possible complication of a dermal filler injection. This complication results are variable depending on the localization of the occlusion and the compromised vessel but always doctors should be aware to recognize this type of complication as soon as possible, to start aggressive treatment to avoid irreversible damages. If the occlusion happens locally, at the injection site, it will result in skin necrosis.

Localized vascular occlusion results from either direct intravascular injection or the compression of the vessels by the injected filler material (10). The patient usually complains immediate pain and acute changes of the skin color, which in cases of an arterial occlusion tends to be pallor and blanched, while in cases of a venous occlusion tends to be redder-more bluish. If the occlusion happens in distant to the injection site, it can result in blindness or cerebral ischemic events. The underlying mechanism is thought to be related to high pressure intra-arterial injection.

The 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 (11). 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 (12). In such events, vascular perfusion must be restored as soon as possible. The procedure must be stopped immediately (23). Inject hyaluronidase to the filler and meanwhile as emergency measures use of acetazolamide, sublingual nitroglycerine, and infusion of mannitol iv. These can be helpful to prevent blindness. An ophthalmologist or oculoplastic surgeon must be contacted urgently.

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 incerebral ischemic events (11). This complication is rare but is serious and life threatening. A doctor can avoid this complication by using the appropriate technique of injection and always aspirate before inject, inject low volume filler and not with high pressure, inject slowly and carefully, use less dense filler. In case of complication and change the color of the area when you inject, and pain stop the procedure immediately. Use hyaluronidase, hot compresses and massage the area. A paste with nitroglicerine 2% to the affected area can promote vasodilatation (Fig. 4).

Fig. 4. *Vascular occlussin.*

Malar oedema

Malar oedema is a complication reaction that is formed in the infraorbital area and tear trough. It is caused from the pressure that the filler material causes to the local lymphatic drainage system in a patient that is predisposed to develop lymphatic drainage problems and the augmenting the barrier of the malar septum (23). It is recommended to use to this area products less hydrophytic and this can be associated with less possibilities for oedema, dyschromia. Malar oedema is a form of chronic oedema that should be taken inconsideration when inject to treat tear trough. It can persist for months and sometimes it can even become permanent if it does not respond to the treatment. Take in consideration to choose a filler that is less hydrophilic to treat this area, to inject it slowly and too deep, to use less product and retouch in another season to avoid this complication. The injection of hyaluronidase for this filler it could be a solution (Fig. 5).

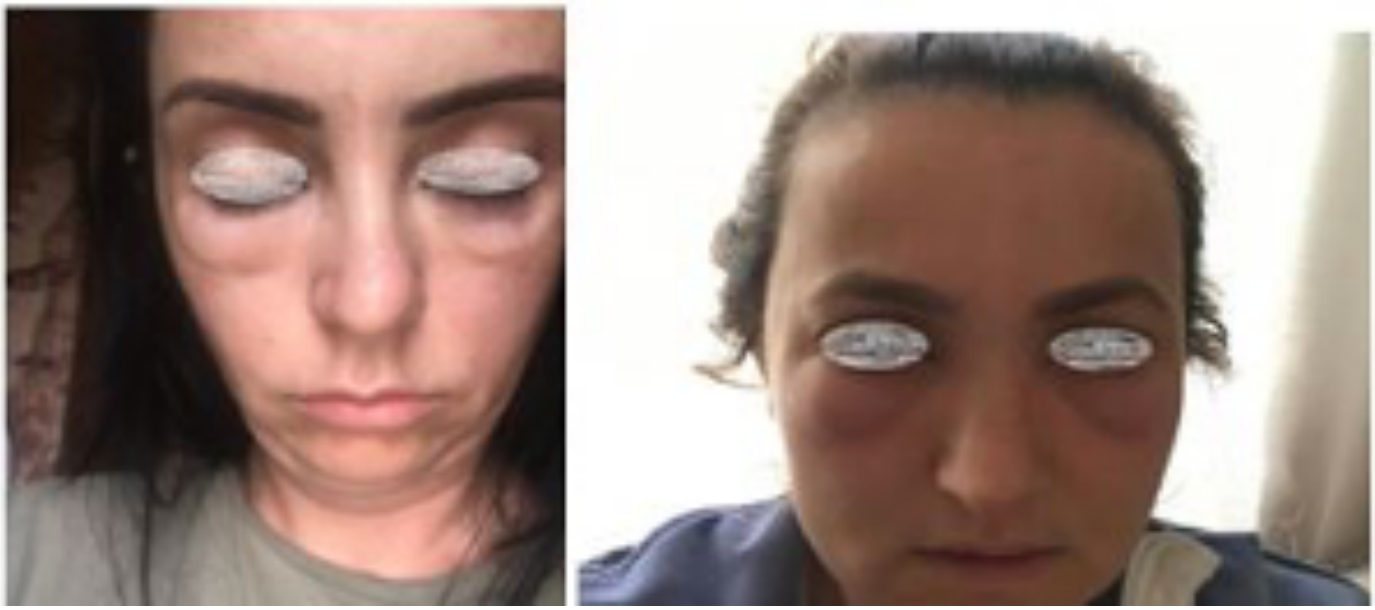

Fig. 5. *VMalar oedema.*

Migration of filler material

A migration of the filler material occurs when the filler is located remotely from the first injection site. Is a rare complication. It can occur at any given time up to several years after the procedure, for as long the dermal filler material (notably semi-permanent or permanent) is present. The reason of a possible migration of filler material, relies on the poor injection technique, high volume of the injected filler, pressure injected filler, overly massaging the area after the procedure, gravity or anti-gravity movements, induced pressure by additional filler placement, lymphatic spread and intravascular injection, or in some rare, documented cases, normal skin ageing (15). The only practical treatment is the removal of migrated filler (Fig. 6).

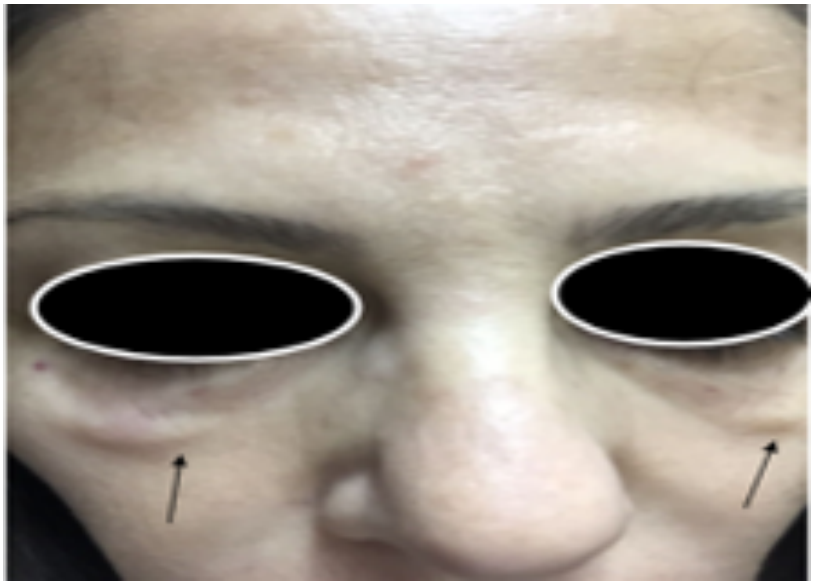

Fig. 6. *Filler migration.*

Conclusions

Hyaluronic acid injection procedures are safe and effective procedures if applied by trained medical personnel (23-30). Therefore, we cannot say that an ideal filler does exist. Every injection procedure (Filler) contains the possibility of developing complications. Having deep knowledge of anatomy and acquiring updated information on aesthetic medicine sub-specialty is a necessity for the medical staff that performs these procedures. Aesthetic medicine is the bridge between medicine and art and should been trusted to experts.

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