Overview and management of fillers complications

Manejo de complicações de preenchadores dérmicos

ABSTRACT

Filler injections are among the most popular cosmetic procedures performed worldwide. Although fillers have a safety profile, there has been a rise in litigation as a result of treatments in the USA. In the Brazilian scenario, the number of non-surgical procedures has increased in the past years, mainly due to the increase of filler options available in the Brazilian market, as well as in the type of professionals allowed to perform injectable procedures. Therefore we sought to review the related literature regarding semi-permanent and temporary fillers adverse effects and outline a practical guide for complications avoidance, diagnosis and management.

Keywords: Granuloma; Ischemia; Esthetics; Hyaluronic Acid; Dermis; Subcutaneous fat; Biofilms; Infection

RESUMO

O preenchimento cutâneo Figure entre os procedimentos cosméticos mais realizados. Apesar de os tratamentos estéticos possuírem perfil de segurança favorável, ocorreu um aumento nos processos jurídicos deles resultantes nos Estados Unidos. No Brasil, o número de procedimentos não cirúrgicos apresentou crescimento nos últimos anos devido não apenas ao maior número de opções de materiais para preenchimento disponíveis no mercado, mas também devido à maior quantidade de profissionais com permissão para executar esses procedimentos. O objetivo do presente estudo foi revisar a literatura, assim como delinear um guia prático para prevenção, diagnóstico e manejo das complicações secundárias ao uso de preenchadores semipermanentes e temporários.

Palavras-chave: Granuloma; Isquemia; Estética; Ácido hialurônico; Dermis; Gordura subcutânea; Biofilmes; Infeção
INTRODUCTION

According to the American Society for Aesthetic Plastic Surgery, more than 13.5 billion dollars were spent on surgical and nonsurgical procedures in the USA in 2015, with nonsurgical procedures accounting for 42% of the total value. While nonsurgical cosmetic procedures have increased by 44% in the past 5 years, injection based procedures have increased by 21%.

In the survey conducted by the International Society of Aesthetic Plastic Surgery, 20 million cosmetic procedures were performed worldwide in 2014, with Brazil ranking third for non-surgical procedures. Nonsurgical procedures accounted for 51% of the total procedures, with botulinum toxin and cutaneous filler injections being the most popular. Botulinum toxin and hyaluronic acid accounted for 71% of non-surgical procedures.

In the United States, with the increased use of soft-tissue fillers, there has been a concomitant rise in litigation asserting harm as a result of treatments. The most common lesion giving rise to litigation was the formation of granuloma or autoimmune reaction.

The number of cosmetic filler options available in the Brazilian market has increased in the past years. Although soft tissue fillers have a very favorable safety profile, between 2003 and 2008 the US Food and Drug Administration has received 930 post-marketed reports of adverse effects, with 823 of those having been classified as severe. Therefore the authors of the present study sought to review the literature regarding semi-permanent and temporary fillers adverse effects, as well as outline a practical guide for avoiding, diagnosing and managing complications.

Pre-treatment considerations: clinical assessment and informed consent

Assessing the patient prior to the injection procedure is vital, not only aiming at evaluating the patient’s expectations, choosing the optimal product, planning the injection, and choosing the injection points, but also evaluating the risks involved.

Patients should be thoroughly queried regarding medical history of bleeding disorders, herpes, auto-immune diseases, pregnancy, allergies, keloid formation and use of medicaments, such as blood thinners (including coumadin and non-steroidal anti-inflammatory drugs), or vitamins/herbal supplements associated with prolonged bleeding – examples include (vitamin E, chondroitin, feverfew - Tanacetum parthenium, ginger, garlic, ginseng, ginkgo-biloba, kava-kava, celery root, and fish oils). Herbal medications should be discontinued 7-10 days prior to the procedure to reduce the risk of hematomas. Regarding patients under use of anticoagulant medication, if it has been is prescribed for a limited period of time, it may be prudent to postpone the injection treatment until the patient has stopped taking the drug. Nevertheless, if the medication has been prescribed indefinitely, the benefit-risk of discontinuing these drugs should be carefully evaluated.

The history of aesthetic procedures should be assessed observing the types of previous aesthetic procedures the patient has undergone and the types of fillers used, as well as previous allergic reaction to fillers or anesthetics.

Overall, fillers should be avoided in case of active adjacent site of infection (intraoral, mucosal, dental or even sinusitis), adjacent inflammatory process, immuno-suppression, allergy to filler components or lidocaine, pregnancy and breastfeeding.

In case of active adjacent site of infection, the procedure should be postponed and the infection should be treated before any injection. If the patient is under dental treatment, Parahitija-wa et al. also recommend to postpone the procedure, due to the fact that dental treatment can cause transitory bacteremia, which is already proven to have systemic impact and lead to diseases, and in theory can also cause colonization of the filler and formation of a bacteria biofilm.

The patient should be advised of the risks in case the physician chooses to perform the procedure during an active infection. The use of prophylactic antibiotic is debatable.

The use of semi-permanent or temporary fillers in an area where permanent fillers have already been injected should be avoided due to the risk of exacerbation or stimulation of nodule formation. Nevertheless, injection in areas different from those where permanent fillers have already been injected could be performed after careful evaluation of the permanent filler’s location assisted by imaging techniques (high-frequency ultrasound – HFUS, optical coherence tomography, MRI and scintigraphy) is carried out prior to the treatment, clearly defining the area that should be avoided. High frequency ultrasound has proven to be the first line tool (quick and cost-effective) for assessing filler site and class (temporary vs permanent).

In complicated cases, MRI seems to be very helpful in correctly evaluating filler migration and identifying subcutaneous abscesses or granulomas.

Photographs should be taken aimed at documenting the patients’ appearance before the procedure, as well as for better analyzing the patient’s areas of concern and eventual asymmetries. The patient’s objectives and corresponding best filler types should be discussed with the patient prior to the treatment, aiming at setting real expectations. The patient should read and sign a free and informed term of consent and the data in Table 1 should be well documented.

Intra-procedure general recommendations

In order to prevent infections and biofilm formation, all makeup and other potential contaminants present on the skin should be removed. In addition, the skin should be cleansed with an antimicrobial preparation, such as aqueous or alcoholic 2–4% chlorhexidine. Chlorhexidine should be avoided in the periocular area due to risk of keratitis. Also, it may be useful to have the patient rinse the mouth with a mouthwash before an injectable procedure to reduce oral microbiota. Oral 0.12%-0.2% chlorhexidine mouthwash was the most effective in reducing tooth biofilm in vivo.

Even though it has not been proven that the use of non-sterile gloves and alcoholic chlorhexidine is insufficient in preventing filler infections, employing sterile technique through-
In the deep dermis, the gray of the needle is not seen, how-
the gray of the needle can be observed and the skin whitens.
right plane for injection. For instance, in the superficial planes,
visual cues help the dermatologist physician to recognize the
minimize adverse events, such as superficial placement. Some
procedure also helps to identify and avoid superficial vessels,
reducing the risk of hematoma. These are mainly influenced by the needle’s gauge,
result from either traces of hemosiderin after vascular lesion and/
or visual distortion of light through the skin due to refraction
causd by the filler25. Fillers should only be injected after the
needle has reached the appropriate depth and injection should be
stopped before the needle is withdrawn. Also, placement in the
correct plane is crucial. For example, semi-permanent fillers, such
as poly-L-lactic acid (PLLA) or calcium hydroxypatite (CaOH),
cannot be placed too superficially and need to be injected in the
subcutaneous or supra-periosteal planes6.

Local massage, incision and drainage, and, in case of HA,
hyalurondcse (HYAL), are treatment options. Also, the use of
Q-switched 1,064nm laser has been reported26.
Calcium hydroxypatite is ideally placed in the subcutane-
ous and may present product migration if the product is placed
superficially or in highly mobile areas, such as the lips. Treatment
options are intra-lesional steroid injection, saline injection followed
by massage, incision and expression or surgical removal7. Also su-
perficial filler placement can lead to lumps and nodule formation.
Please, refer to the Nodules and the Lumps sections.

Managing adverse events
I) Early reactions (from a few days to several
days)
A) Local reactions
Local reactions can be related to the injection alone,
including local inflammation, hyperemia, tenderness, and he-
matoma. These are mainly influenced by the needle’s gauge,
sodes/year). Acyclovir 400mg three times per day for 10 days or valacyclovir 500mg twice per day for 7 days can be employed, starting 2 days before the procedure (28).

F) Infection

Early-onset infections arise with induration, erythema, tenderness and pruritus, and might be indistinguishable from transient post-procedure response. Fluctuating nodules and systemic symptoms (fever, chills) can occur later on. Skin infections are usually related to resident flora (Staphylococcus or Streptococcus spp.) introduced through injection. Microbiological culture should be performed and culture-appropriate antibiotic treatment installed. Abscess should be drained. In longer lasting infections or poor response to antibiotics, atypical infection (i.e. Mycobacterium spp.) and biofilms should be considered. In these cases alternative antibiotic may be necessary.

G) Acute hypersensitivity

Foreign body fillers can trigger immune response. Hypersensitivity reactions can range from mild redness to anaphylaxis. The incidence of hypersensitivity reaction related to HA is around 0.6%. About 50% (4) of these cases are transient and resolve within 3 weeks. In a prospective, randomized study, 433 patients injected with NASHA HA were evaluated using skin testing, IgE and IgG antibody serology, and histopathology studies. No detectable allergenicity (Type I) or delayed hypersensitivity (Type IV) was reported (29). Use of anti-histamines, non-steroidal anti-inflammatory drugs (NSAIDs), intralasional steroids, minocycline and hydroxychloroquine have been reported. Hyaluronidase may help removing the core of the inflammation (30).

H) Lumps

Lumps are caused by excessive HA, superficial product placement, areas of thin skin (i.e. eyelids) or migration due to muscle movement (i.e. lips) (22). Treatment options comprise aspiration, incision and drainage or removal by HYAL injection in case of HA (24). It is important to note that this reversion ability of HA is unique (6). Previously diluted HYAL and lidocaine can be used to dissolve the lump (31).

In a retrospective study conducted in Brazil, 50 patients who underwent HYAL injections to treat complications or unesthetic results following HA injections were given doses of this enzyme ranging from 40 to 160 Units per anatomic area (32).

I) Vascular complications

The most feared complication among those caused by the use of dermal fillers is injection-induced necrosis, which is caused by vascular occlusion or trauma. Impending necrosis was described with different filling materials with an estimated frequency of 0.001% of total procedures performed (33).

First and foremost, a thorough knowledge of the facial vascular network is crucial, especially when treating areas with terminal blood vessels, such as the glabella and the nose. Among risk factors for intra-arterial injection are related to: 1) the injected areas: high-risk areas include areas near the facial artery, angular artery along the nasolabial fold, nose and glabella. The glabella has tenuous blood supply, originating in branches of internal and external arteries, having a close connection with the eye’s vascular system. The facial artery becomes superficial close to the pyriform fossa at the apex of the nasolabial fold. Therefore in this area, the filler placement should be carried out deeply in the supra-periosteal area with a needle, or more superficially, with a blunt cannula; 2) large volume of injection; 3) small sharp needles, that are more likely to penetrate the vascular lumen, as compared to larger bore needles and cannulas. Nevertheless, blunt cannulas may reduce – but not eliminate – the risk of vascular lesion; 4) previous scarring, which stabilize and immobilize arteries in place, making them easier to penetrate with needles; 5) composition of the filling material: permanent fillers cannot be dissolved and can obstruct the lumen (34). The filling material primarily implicated in blindness is fat. Nonetheless, other substances, such as collagen, CaOH and HA, have also been reported to have caused blindness (30).

The typical clinical appearance following HA filling caused ischemia is transient blanching (duration of a few seconds), followed by a livid pattern or reactive hyperemia (minutes), black-bluish discoloration (ten minutes to hours), blister formation (hours to days), and cutaneous necrosis and ulceration (days to weeks).

Preventative measures include the use of small volumes, greater than 27G blunt cannulas, and slow injection. Aspiration prior to injection does not ensure vascular safety, but should be performed.

Clinical symptoms that should prompt the physician to immediately stop injecting are: pain, skin blanching or color changes (livedo, blue or gray color) in the distribution of the regional blood vessels. Another cue is observing the blood return after digital compression of the area. Return to normal color takes 1–2 seconds. Slower capillary blood return may be a sign of arterial insufficiency (35). Ice and epinephrine may mask the signs and symptoms of arterial insufficiency.

Hyaluronidase is considered the backbone of vascular occlusion treatment (5, 34). It consists of a soluble protein enzyme that hydrolyzes both natural and cross-linked HA. Even tough actual need of intravascular injection has been reported (34), diffuse injection of HYAL into the tissues affected by ischemia seems to be enough in most cases, for HYAL can easily cross facial planes and tissue structures by affecting the HA of the dermal matrix (35, 36).

A recent consensus recommendation for impending necrosis treatment included (33):

1) The use of significant amount of HYAL in the area of necrosis. It is important to flood the area, as soon as possible. A minimum of 200UI is recommended. No test is needed to assess impending necrosis. Early HYAL injection reduced the size of necrosis in animal experiments, when compared to late injection (24hs) (33). Also, the nature and quality of the dermal filler are important considerations for HYAL effectiveness. Hyaluronidase hydrolyzes Restylane® more quickly and with smaller volumes when compared to other HAs (Juvederm®, Volbella®, Prevelle® and Belotero®) (11, 33, 36–38). If no improvement is seen in 60 min, the injection should be repeated.
2) Vigorous massage and warm compress (for 5–10 min, every 30–60 min).

3) Massaging topical 2% nitroglycerin (NTG) paste on the area immediately on suspicion of necrosis and up to 2–3 times daily is an option. The patient should be lying down during the application of NTG to prevent syncope by fall of blood pressure due to systemic vasodilation. In addition, nitroglycerin paste is contra-indicated in patients taking PGE2 medications such as Viag® (Pfizer, NY, USA). Alternative protocol: nitroglycerin paste under occlusion for 12 hs, followed by a 12-hour interval before applying again.

It is important to highlight that the use of topical NTG is controversial, since according to the preliminary data in animal models, topical NTG was not effective and, in theory, could worsen the picture with dilation of the arterioles, further propagating the product into the smaller capillaries, causing increased dermal ischemia.

Nitroglycerin is not available in Brazil.

4) Introduce oral aspirin regimen: two 325mg pills per day, usually for 1 week to prevent further clot formation. Since in Brazil available aspirin dosages are 100mg and 500mg, patients can take 500–600mg daily for 1 week.

5) Daily patient follow-up: HYAL and NTG can be continued as needed for the following few days. If improvement is observed, NTG massages can be stopped. If there is no improvement or progression, HYAL, NTG and aspirin should be repeated daily.

6) Daily low-molecular weight heparin, prostaglandin E1, systemic anticoagulation, hyperbaric oxygen therapy, and sildenafil have been recommended as other treatment options. Recommendations of 8ml sterile water for injection (SWI) and 30 units of hyaluronidase were used successfully.

7) Patient aftercare should ensure: proper wound care with daily dressings and wound coverage with ointment to prevent crusting, skin hydration, debridement of necrotic skin and secondary infection prevention.

Even though the use of HYAL for the reversal of vascular complications is “off-label”, the prompt diagnosis and immediate treatment with this enzyme is crucial.

II) Late onset reactions (from weeks to years)

A) Nodules

In a 5-year retrospective review, 14 complications were reported out of 2,089 injectable soft-tissue filler treatments (PLLA, HA and CaOH), with nodule or granuloma formation reported out of 2,089 injectable soft-tissue filler treatments this series (2.6% of treated cases). Delayed reactions to HA-based fillers are estimated to occur in approximately 0.02% of patients. In case of some injected materials, the desired tissular response, the clinical significance of granulomatous inflammation is normal and in case of some injected materials, the desired tissular response, the clinical significance of granulomatous inflammation is normal and in case of some injected materials, the desired tissular response, the clinical significance of granulomatous inflammation is normal.
Inflammation should be based on its extent, severity and long-term progression of the response (25). Clinically, granulomas may be accompanied by discomfort, persistent or transient edema, erythema and periods of crisis and regressions. Also, when all implantation sites develop a similar scenario, the differentiation from a nodule caused by filler misdistribution is easier (45).

In the absence of fluctuation and systemic symptoms, histologic and/or microbiologic examination is required to rule out infection. Histopathology is useful not only for the diagnosis of granuloma, but also for the recognition of the implant’s nature (48). Permanent fillers present higher risk of granulomatous reaction (49). Less frequently, granulomatous reactions have been described after CaOH (50, 51), PLLA, and HA injections (45).

Intralesional steroid is the recommended treatment for granuloma (6). Usual dosage would be 5–10mg/cc, repeated 4–6 weeks later, according to necessity (9). In case of HA, HYAL injection may be a therapeutic option. Massage, oral steroids (0.5–1mg/kg/day up to 60mg/day), oral minocycline (anti-inflammatory, immunomodulating and anti-granulomatous properties), pulsed dye laser, intralesional bleomycin and intralesional 5-fluoracil have been reported as additional therapeutic tools.

Antimalarials (hydroxychloroquine 4–6.6mg/kg/day) have anti-inflammatory and immunoregulatory properties, inhibiting phospholipase activity and blocking several pro-inflammatory cytokines (52). Retina evaluation should be performed periodically. Anecdotic reports have suggested colchicine, anti-histamines and cyclosporine A use in refractory cases. Surgical excision should be avoided during active inflammatory processes or in patients with multiple and/or extensive lesions, due to the risk of filler migration, fistulae formation, scars and persistent granulation tissue (52). The prognosis is usually good for temporary filler granulomas (49).

B) Infection

Late infection typically manifests as tingling sensation followed by swelling 8–12 days after injection. Usually common skin pathogens, such as *S. aureus* are associated. Symptoms are usually described as abscesses, abscess-like nodules, foreign-body nodules or delayed-onset reactions. Fluctuation and systemic symptoms help diagnose infection (25). Nevertheless, in face of a firm, tender mass or nodule, which develops from 2 weeks after the procedure, atypical infection and mycobacteria should be
considered in the differential diagnosis (53). Biological material from biopsy or fluid aspiration should be sent for staining, and for alcohol-acid resistant bacterial, fungal and bacilli culture25.

B1) Biofilms

One factor is a common denominator for all biofilm implants: a bacterium or infective microorganism is necessary to contaminate the injection for the formation of a biofilm to begin. Biofilm is a glue-like matrix secreted by bacteria, forming a medium in which other bacteria thrive, while evading antibiotics and the immune system11. The colony-biofilm becomes antibiotic-resistant by lowering its metabolism, also being protected from phagocytosis by an extra-polymeric system membrane41. Chronicity and recurrence of infection are hallmarks of biofilms42.

Implanted foreign bodies can become infected with skin contaminants during a procedure, or be colonized by direct or hematological spread of an infectious agent39. Biofilm may exist in a dormant state and be activated by local trauma, manipulation and injections. Once the biofilm is activated, it can become an acute purulent or a sub-acute course infection, with granulomatous response to the activated biofilm. The active infection can be controlled with antibiotic therapy, however the underlying biofilm can generate recurrence.54

In addition to being difficult to treat, biofilms can be involved in delayed-onset skin reactions to fillers, such as granulomatous inflammation, abscesses, nodules or recurrent infection7,9,11. A review of hypersensitivity reactions reports suggested that most of the reactions described were due to infectious processes56.

Biofilms are difficult to diagnose, due to the fact that most microbiological cultures from biofilm-infected tissues are negative. Some bacteria are difficult to grow using traditional methodology, given that their slow-growing nature is often overgrown by faster growing bacteria. Molecular studies, such as PCR and fluorescent in situ hybridization (FISH) are more accurate methods52,57. Finding the location of the material for biopsy or HYAL injection in case of HA, can be performed by ultrasonography, computed tomography scan (radiopaque material), MRI (non radiopaque implant)55. Positron emission tomography scans may help identify loci of infection. Sufficient tissue from biopsy should be obtained for bacterial, fungal and mycobacterial cultures.

Some authors suggest avoiding additional injections in the region of the implant, as well as dental procedures and facial trauma for 2 weeks following dermal filler injection42. Even tough, the use of prophylactic antibiotics is debatable and it may be reasonable for certain large-volume filler injections34.

Since the risk of biofilm should be considered in late-onset reactions, the use of oral steroids and NSAIDs should be avoided. Biofilms may require a 32 times higher amount of antibiotics than that required for killing planktonic bacteria. The recommended treatment should consider the association of at least 2 broad-spectrum antibiotics such as a quinolone (i.e. ciprofloxacin) and a third-generation macrolide (i.e. clarithromycin) for up to 6 weeks7,21. Macrolides have superior efficacy in treating biofilms, since they accumulate in the subcutaneous fat51. In addition, since bacteria are bound to the foreign material, complete resolution is difficult without its complete removal52. Therefore use of HYAL should be considered in case of HA or excision (11). Another reported option is the use of intralosional 5-FU, which has been shown to interact with a bacteria regulatory gene (4rR) that inhibits biofilm formation55.

C) Filling material migration

Filler migration can occur early or late, regardless of the type of the filling substance. Several mechanisms, such as poor technique, high volume of filler injected, filler injected under pressure, massageing after filler injection, muscle activity, gravity, pressure-induced displacement (i.e. injection of additional filler), lymphatic and intravascular spread (more related to permanent fillers) have been related12,46. Imaging and histopathology techniques are of assistance in the correct diagnosis.

Hyaluronidase (HYAL)

It is important to point out that HYAL is not commercially available in Brazil. The dosage is highly variable, depending on the treated area and volume of HA placed, ranging from 25UI (in tear though) to 1,500UI (in the case of vascular occlusion)11. Hyaluronidase can be diluted in saline or local anesthetics, however the resulting pH may alter the efficiency of the enzyme. It may be injected slowly and directly into the site of HA injection56. Massaging is important for obtaining the therapeutic effect. Hyaluronidase treatment should be performed as soon as possible. In a review study, if HYAL were injected within 2 days, full recovery was expected. On the contrary, if injection of HYAL were delayed, there was an increase in the risk of scar and tissue defect formation58.

Adverse reactions to HYAL are uncommon. Urticaria and angioedema are reported in less than 0.1% of patients and have occurred after retrobulbar or intravenous injections5. Therefore, some authors suggested that before applying HYAL, a sensitivity test should be performed injecting 3 units intradermally, with the patient being observed for at least 20 minutes. Local swelling indicates a positive reaction and may reflect sensitivity to animal protein or to preservative or cross-reaction with bee venom32,24,36,41.

Hyaluronidase has a half-life of 2.1 minutes, caused by inactivation in the kidneys and liver. The most common drug interactions occur with furosemide, benzodiazepines, and phenytoin, which are incompatible with HYAL. Hyaluronidase should not be used to enhance the absorption and dispersion of dopamine and/or alpha agonist drugs. Also, HYAL may accelerate the onset, shorten the effect’s duration, and increase the incidence of systemic reactions to local anesthetics. Large doses of salicylates, cortisone, ACTH, estrogens or antihistamines may require larger amounts of HYAL for an equivalent dispersing effect (31).

The dermal filler’s nature and quality are important factors for the effectiveness of HYAL in case of an adverse effect. Hyaluronidase can more quickly hydrolyze Restylane® (Q-med) as compared to other HAs (Juvederm® - Allergan, Volbella® - Allergan, and Belotero®). Juvederm® takes significantly longer to disperse than Restylane®11,33,36-38.
Hyaluronidase should not be used in case of infection, due to the risk of spreading the infected material diffusely\textsuperscript{11}.

**CONCLUSION**

Dermal fillers are among the most common aesthetic injectable procedures. Although considered very safe, adverse events may occur. Careful patient assessment, adequate therapeutic planning, and an accurate technique are crucial for achieving the best treatment outcomes. To be prepared to assess and handle possible adverse effects promptly is of paramount importance.

**REFERENCES**


