ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 10, Issue, 11, pp. 42285-42291, November, 2020
https://doi.org/10.37118/ijdr.20426.11.2020

RESEARCH ARTICLE OPEN ACCESS

COMPLICATIONS OF INJECTABLE HYALURONIC ACID AS A SOFT-TISSUE FILLER: A CURRENT OVERVIEW

Iasmin Freitas Pimentel Pequeno*[1] and Francisca Inês de Sousa Freitas [2]

[1]DDS. Postgraduate in Oral Surgery and Specialization student in Orofacial Harmonization at Unifuturo, Paraiba – Brazil
[2]PhD. Professor at Pharmaceutical Sciences Department – Universidade Federal da Paraiba – Brazil

ARTICLE INFO

Article History:
Received 03rd August, 2020
Received in revised form
16th September, 2020
Accepted 14th October, 2020
Published online 30th November, 2020

Key Words:
Adverse events, Complications, Dermal Fillers, Hyaluronic Acid Filler, Injectable Hyaluronic Acid.

Corresponding author:
Iasmin Freitas Pimentel Pequeno

ABSTRACT

Hyaluronic acid filler is an injectable product for soft-tissue augmentation that proposes an improvement of facial aesthetics and, therefore, rejuvenation; it became popular for its favorable aesthetic outcomes, great biocompatibility and possibility of reversion. However, with the increasing number of procedures each day and more injectors, not always qualified, being licensed to perform them, the quantity of adverse events related to this filler material has intensified. In view of that, this article aims to make a research in the current literature about the most frequent complications of injectable hyaluronic acid fillers. An intense bibliographic search was accomplished using the keywords related linked to the subject on electronic scientific databases. Publications from 2015 to 2020 in English, Portuguese and Spanish language were selected, totalizing 46 articles consisting in case reports, reviews and clinical researches. The main adversities referred in the studies were immune responses, formation of nodules, infections, and vascular complications resulting in visual loss and necrosis. Professional injectors must be enlightened about such complications, being able to identify, prevent and successfully remediate them, mastering not only the injection techniques, but also the human anatomy and physiology, the properties of the chosen material and its correct indications to suit each patient.

Citation: ***Iasmin Freitas Pimentel Pequeno and Francisca Inês de Sousa Freitas.*** "Complications of injectable hyaluronic acid as a soft-tissue filler: a current overview*", International Journal of Development Research*, 10, (11), *42285-42291*.

INTRODUCTION

The seeking for rejuvenation and adhesion to beauty standards has always been present in human society, however, in the recent years, the obsession for perfection and constant need to increase self-esteem by going through aesthetic procedures have been even more frequent as a result of the strong social media marketing that deeply influences behaviors and lifestyles. Therefore, the access to less invasive cosmetic procedures has quietly increased, especially in countries like Brazil, where more professional categories, such as dentists and pharmacists started to be legally licensed to perform those treatments, being no more restricted to physicians. The popularization of non-invasive cosmetic procedures have also enlarged the number of adverse effects and iatrogenic consequences related to them (Robati et al., 2018; Castro and Alcantara, 2020). One of the main non-invasive cosmetic procedures include dermal fillers injection for soft-tissue augmentation in order to restore age-related facial volume loss, correct anatomic asymmetries, reduce wrinkles and promote some facial rejuvenation.

According to the American Society of Plastic Surgery, in 2014 fillers made of hyaluronic acid (HA) constituted 78.3% of all used injectable dermal fillers (Abduljabbar and Basendwh, 2016; Shoughy, 2019). Hyaluronic acid is a natural substance that exists in the extracellular fluid of living beings. Characterized as extremely hydrophilic and water-soluble, features that allow it to attract large amounts of water, which consequently increase skin elasticity and hydration. It is chemically defined as a non-sulfated glycosaminoglycan polysaccharide, made of linear polymeric dimers of glucuronic acid N-acetyl glucosamine, figuring as an integral part of the extracellular matrix, abundantly found in numerous connective tissues, for example: the skin (Maia and Salvi, 2018; Wang et al., 2020b). The commercial presentation of injectable HA consists in a sterile syringe within an uncolored gel that can also show up in formulations mixed with lidocaine to minimize pain. HA is considered a moderate-duration kind of filler because it can be totally reabsorbed by the human body, having, for that reason, non-permanent aesthetic results and being capable of lasting from 6 to 18 months, depending on the

HA concentration, amount and degree of cross-linking, and particle size of each product. Although, it is as well discussed that determining the mean duration of HA is a complex thing, regardless of the chosen type and brand, it depends as well on the skin condition, age and habits of the patient, volume of material injected and the distinct levels of dermal application: if placed superficially, middle or deeply (Mansouri and Goldberg, 2015; Wortsman, 2015; Scardovi et al. 2017). HA injectable fillers can be obtained from both animal and non-animal sources, being more often produced biosynthetically by bacterial fermentation. Each type of HA-based material differs in the methods adopted to crosslink their dimers, the chain extension of crosslinking, also the degree of purity, concentration level, uniformity and dimension of the particles. All of these features show relevant influence in the clinical outcomes of the product; since increased crosslinking and concentration, for instance, elevate the viscosity and elasticity as well as the resistance to degradation by natural hyaluronidase, making the material last longer in the body. Additionally, the more concentrated is the hyaluronic acid and the larger are its particles, the more hydrophilic the product will be, increasing tissue swelling after injection (Mansouri and Goldberg, 2015; Scardovi et al., 2017; Maia and Salvi, 2018).

The HA has a great compatibility with the human tissues, not commonly producing immune reactivity, and showing reversibility when the hyaluronidase enzyme is used in the injected area, what makes HA a suitable product for many professional injectors for its safety, effectiveness and predictable aesthetic results (Abduljabbar and Basendwh, 2016; Robati et al., 2018). Despite all the mentioned benefits, the injection of dermal fillers is considered a blind procedure as the injector is incapable to verify exactly where the filler is placed, being the success of the treatment very multifactorial. With these characteristics, injectable fillers become likely to cause numerous complications, being adverse effects not so uncommon: one study of 286 patients injected with hyaluronic acid gel registered a complication rate of approximately 5% (Wortsman, 2015; McCracken et al., 2016; Robati et al., 2018;). Based on the information above, this article aims to make a research in the current literature on the most frequent complications of injectable hyaluronic acid fillers for that professional injectors must be absolutely conscious and enlightened about such adversities, being able to identify, prevent and successfully remediate them.

MATERIALS AND METHODS

An intense bibliographic search was performed from June to October of 2020 using the keywords “Hyaluronic acid filler”, “adverse events”, “injectable dermal filler”, “soft tissue filler”, “complications”, and “injectable hyaluronic acid” in the following electronic scientific databases: PUBMED (US Library of Medicine), SciELO (Scientific Electronic Library Online), BVS (Biblioteca Virtual emSaúde) and Google Scholar. Publications from 2015 to 2020 in English, Portuguese and Spanish language from scientific journals were included.

RESULTS AND DISCUSSION

Cosmetic fillers have been frequently used to restore facial volume due to aging process, correct asymmetries, improve facial harmony and promote rejuvenation. Recently, with social media influence and diffusion of new aesthetic and beauty standards that praise minimally invasive cosmetic procedures, the search for filling treatments has intensified. Accordingly to the International Society of Aesthetic Plastic Surgery –ISAPS in a survey performed in 2018, the number of non-surgical procedures using hyaluronic acid has increased in 11,6% since 2017, being the United States the country which performs them the most, followed by Brazil. Therefore, the HA filler is currently the main used material to enhance volume in soft tissues because of its impressive biocompatibility and capacity of reversion. However, despite the referred benefits, the possibility of adverse effects and negative consequences may occur in response of the escalating number of procedures. (Parada et al., 2016; Gutmann and Dutra, 2018).

For this research, 46 articles dating from 2015 to 2020 were selected, consisting principally in case reports, clinical trials and bibliographic reviews related to complications of injectable HA fillers. Considering that there is relatively few clinical evidence on the correct approach for adverse events related to inject able HA, and many of these incidents may be unregistered in the scientific literature, Almeida et al. reported in 2017 the occurrence of a panel meeting including 25 Latin American experts from multiple specialties, aiming to debate the adversities of the inject able HA usage and attempting to come up with better understanding of such problematic episodes based on their clinical experiences, making recommendations and establishing a treatment for each complication via consensus process. Hence, considering that time is a crucial information regarding the recognition and reversion of adversities, the panel consensus categorized the incidents by how long they take to appear, being divided as: of immediate onset, with signs and symptoms showing up until 24 hours after the injection; of early onset: from 24 hours to 30 days post application; and of late onset: appearing after 30 days, at least.

The principal immediate complications can emerge as pain, itching, edema, hematoma, ecchymosis, allergic reactions, paresthesia, and vascular damages like embolization and arterial occlusion. The main adverse events that show up until 30 days can be ischemia, necrosis, telangiectasia, persistent erythema, Tyndall effect, also systemic changes in consequence of infection, inflammation, local scars and skin irregularities as nodules. The late adversities can be telangiectasia, persistent erythema and persistent late edema, keloids and nodules (Almeida et al., 2017). Some complications such as pain, erythema, itching, swelling and ecchymosis are more frequent and self-limited, lasting about 1 week and needing no big intervention. Pain is a common event in any injectable procedure and in order to reduce it the injector can apply topic anesthetic agents or do infiltrative nerve blocks, try vibratory distractions, do previous ice applications, prefer the use of small needles and blunt-tipped cannula (Abduljabbar and Basendwh, 2016; Daher et al., 2020).

Swelling, edema and erythema happen in about 80% of the injections and are local inflammatory responses in consequence of the tissue injuries that can last for many hours to days. They are normal reactions, however can get worsen if preceded by an incorrect application technique or the use of a more dense AH product in the wrong placement, for example.

Applications of ice, use of oral anti-histamines and short time prednisone have been told to minimize swelling and edema. Hematoma is a common adversity caused by the rupture of blood vessels during the penetration of the needle and can be reduced once the injector has a good anatomic knowledge of the face vascularity and does the procedure under good illumination. Adopting the usage of blunt-tipped cannulas is efficient to decrease bleeding, hematoma and pain due to minimizedintra-tissue trauma and the need of less quantity of punctures. Fillers with lidocaine in the formula are helpful reducing painful sensations, but can cause more edema and bleeding for that it promotes vasodilatation, as well as patients using vasodilation medication or with coagulation disturbs should avoid injecting procedures (Parada et al., 2016; Gutmann and Dutra, 2018).

In a study performed by Scardovi et al. 2017, using one brand of injectable HA in 40 patients to fill nasolabial folds, no adverse reaction related to the product itself was observed. Nevertheless, some complications related to the injection technique were reported in 13 patients (32.5% of the treated cases), of which consisted in bruising (11), hardness (3), edema (2), inflammatory signs (2) and nodule (1). Showing that the success of the treatment is very operator-dependent, once the product is especially biocompatible.

Tyndall Effect: Tyndall effect is a visual phenomenon caused by the superficial placement of HA filler or its application in large volumes, being more likely to occur in areas where the skin is thinner. Can be mistaken for a slight but deep bruise as it generates a bluish discoloration in the affected area, possibly in consequence of the light refraction originated by the product localization. It can be frustrating for patients and delivers a poor aesthetic outcome, possibly leading to anxiety and lower self-esteem. This failure can be corrected by using hyaluronidase to dissolve the material, but a removal under surgical excision or aspiration can also be performed (King, 2016; Gutmann and Dutra, 2018).

Immune Responses: Immune responses generated by dermal fillers can range from a slight redness to anaphylaxis. Even though incidence of hypersensitivity reaction related to HA is around 0.6% , these reactions can lead to subacute or delayed complications, such as granulomas. A half of these cases are transient, being normally solved in no more than 3 weeks. Wang et al. (2020a) in a review study on hypersensitivity caused by cosmetic injections observed 57 cases of hypersensitivity of which 46 were related do HA applications. Bittermann-Deutsch et al. (2015) reported 5 cases of delayed immune-mediated effects due to HA fillers, in which symptoms started 48 hours to 7 months after injection, having all patients be treated with corticosteroids and antibiotics. Chung et al. (2020) did a systematic literature review about delayed inflammatory responses after HA filler injection, to estimate the incidence of those reactions, and noticed that the incidence of both delayed and immediate types is so low that a pretreatment skin test is not mandatory before using the HA fillers approved from regulatory and sanitary agencies. Whilst Fan et al. (2016) reported a case of acute anaphylactic reaction that was successfully managed and happened 3 days after HA filler injection in the temporal, tear through, zygomatic, nasal and mentalis region. Pérez et al. (2019) reported a case of granulomatous foreign body reaction after a nasal injection with HA that occurred 5 years after the procedure and was treated with surgical excision.

Similarly, Pozuelo et al. (2020) observed multiple nodules in the lips of a patient 5 months past the HA infiltration. The histopathologic results showed compatibility with foreign body granulomatous reaction, which is a rare delayed adversity that has been associated with bad injection technique or hypersensitivity reactions that can be triggered by impurities developed during the bacterial fermentation process to produce the Hyaluronic Acid. HA fillers can be obtained from both animal and non-animal origins, but the risks for immune mediated consequences are reduced when it is produced biosynthetically by bacterial fermentation due to less presence of food allergens. In a laboratory research aiming to evaluate the adverse effects of various distinct fillers successively applied in the same area using 3 types of products in lab rats, Chung et al. (2019) observed a granulomatous reaction in the combined fillers areas, identified as different micro-implants in the same biopsy, suggesting that the use of dissimilar materials in the same placements can induce more undesired reactions.

Formation of Nodules: Among all complications after HA fillers, the occurrence of nodules is sort of frequent. In daily practice many terms are used to describe a "nodule," as they can be defined as a mass, lump, induration, abscess, or granuloma. Even if they have distinct meanings, they are not effortlessly distinguished from each other, frequently needing a confirmatory diagnostic examination (Modarressi et al., 2020). Said that, in a retrospect analysis of oral lumps and bumps caused by dermal fillers in an Oral Pathology Service, Martin et al. (2019) observed that the main material causing those alterations was HA-based, but the majority of the provisional clinical diagnosis referred common oral lesions, such as salivary gland diseases, instead of dermal filler injections; finally the confirmatory diagnosis were defined after histopathologic examinations. Modarressi et al. (2020) reported 26 cases of individuals that underwent biopsy for analysis of facial nodules formation more than 3 months after different types of filler injections, aiming to make a correct diagnosis of the lesions. It was observed that of those injected with HA, only 2 were granulomatous nodules, while 4 were non-granulomatous ones.

Infections: Early-onset infections arise with erythema, tenderness, itchiness and might be indistinguishable from transient post-procedure inflammatory response. Fluctuating nodules and systemic symptoms like fever and chills can occur subsequently. Infection as an adverse event happens in consequence of the introduction of pathogens through the injection by the operator, once that the product comes in sterile syringes. These events are usually linked to resident flora microorganisms such as *Staphylococcusspp*. or *Streptococcus spp*. Nevertheless, Alshaer et al. (2018) has reported a successfully managed case of a filler infection with Brucella, and Shin et al. (2017) described an unusual infection with Aspergillus in a patient presenting a chronic inflammatory nodule with abscess formation after a filler injection. Furthermore, other atypical infection with *Mycobacterium spp*. as well as late formation of biofilms should be concerned. Horriat et al. (2020) described a case affected with facial granulomatous nodules and fungal/bacterial infection after HA injections in multiple sites. The patient exhibited hypersensitivity reaction one month after the procedure, consisting in facial edema, erythema, itchiness and mild fever. Subsequently developed verrucous granuloma-like skin lesions in the areas injected with HA. *Escherichia coli*, *Enterococcus faecalis*, and *Staphylococcus epidermidis*were found infecting

the mentioned lesions. The suggested mechanisms in this case included inflammatory foreign body reaction and pathogen contamination. Finally, anti-fungal, antibacterial therapy and local excision were adopted to manage the situation.Hyaluronidase should not be used in case of infection process of the treated area, due to the risk of spreading the infected material diffusely, however, when necessary it can be administered with systemic antibiotics (Almeida and Saliba, 2015).

Infectious episodes can be increased because of an improper disinfection of the skin and use of non-sterile ice before the injection, an operator adopting poor hygiene measures during the procedure, a possible decreased general immunity of the patient, and the presence of pathogens contaminating objects like gloves and cannulas, for example. In addition, the skin should always be cleansed with antimicrobial solutions, such as alcohol or chlorhexidine, and recurrent use of antiseptics locally throughout the injection process should be adopted to prevent the mentioned adverse event (Parada et al., 2016; Shin et al., 2017). Goodman et al. (2020) suggest that in the current COVID-19 pandemic, including the use of mouth, nose, and eye antiviral irrigation prior to the procedure may become commonplace to help avoiding contamination.

Herpes Activation: The risk of herpes activation following dermal filler injection due to direct damage to the skin nerves caused by the needle, with subsequent tissue manipulation and inflammatory reaction is estimated to be less than 1.45% (Parada et al., 2016). Although, this condition can also appear due to systemic stress or immunosuppression. Wang et al. (2020b) observed a case of herpes activation in a patient with complaint of erythema, crusted papules, pain and swelling on the nose for 4 days after the injection of HA. The patient reported no herpes outbreaks history though and the case was managed with antiviral therapy with Acyclovir.

Vascular Complications: Vascular complications can result either from direct intravascular injection or the compressive action originated by greater volumes of filler material against the local vessels, causing vascular occlusion, embolism or compression. These problems are not usual, however can lead to serious events such as necrosis, blindness and even cerebral infarction. The main high-risk facial zones for skin necrosis and embolization are the glabella, which has no substantial blood supply (having a real close relation with the ocular vascular system), forehead, nasolabial fold, nasal ala and dorsum of the nose. Comprising, foremost, anatomic parts supplied by the internal branches of the carotid artery, areas that have extensive vascular anastomoses and locations where the arteries emerge from the cranial foramen (Almeida et al., 2017; Abduljabbar and Basendwh, 2016; Habre et al., 2016). In a study review with meta-analysis, Sito et al. (2019) verified 93 cases of vascular complications in consequence of cosmetic injections, being blindness the main outcome, resulting from the injury to ophthalmic and retinal arteries and showing non-recovery in 72% of the cases. It was also noticeable that HA-based fillers figured as the main products causing vascular occlusions. Shoughy et al. (2019) reported a case of immediate visual loss following HA injection to the glabellar area, accompanied by weakness of the left arm, which highlights the possibility that the injection force applied was high and could have led to cerebrovascular embolism. Whereas Yao et al. 2019 registered an ophthalmic artery occlusion combined with superior sagittal sinus thrombosis caused by HA filler injection into the forehead, experiencing sudden vision loss and severe pain in the left eye in addition to headache, all symptoms appeared immediately after the injection. Hu et al. (2016) verified the occurrence of visual loss in a patient 7 hours after receiving HA infiltrations in the forehead that resulted in a posterior ciliary artery occlusion and an embolic involvement of the facial artery branches.

In a retrospective study of 21 patients, Yang et al. (2019) observed 15 cases (71%) of ophtalmoplegia, which consists in paralysis of the eye musculature, after ophthalmic artery occlusion caused by injectable dermal fillers. It is remarkable that ocular motility recovers spontaneously in most patients, in opposition to visual loss, that is more often irreversible. Another kind of ocular compromise caused by fillers is their migration to the orbit, as discussed by Hamed-Azzam et al. (2020) showing 7 patients that presented orbital symptoms after the injection and surprisingly discovered that had filling product inside their orbits. As the site of application is far from the migratory placement of the material, the diagnosis of orbicular filler migration can be complicated, needing several examination.

As mentioned before, the most dangerous facial zones for serious vascular complications are the upper third of the face (comprising glabella and forehead) and the middle third (especially in the nasal area). Nonetheless, Goodman et al. (2020) have stressed the risks of injecting into the perioral and periorbital mimetic muscular layer. Considering its anatomical and physiologic features, it can result in product clumping, displacement, and tendency to late nodularity and swelling, as well as intravascular injection as compared to injection in other layers of the face, once the large vessels of the inferior and superior labial arteries in addition with the mental and submental are potential embolic targets. Studies demonstrate that intra-arterial hyaluronic acid (HA) filler injection is the most likely etiology for filler-induced tissue necrosis observed clinically (Chang et al., 2016). Being individuals that undergone rhinoplasty surgery more susceptible to suffer skin necrosis after injections in the nasal area, as seen by Robati et al. (2018) in a retrospective study who identified patients that suffered skin necrosis after HA injections in the nose, having all of them been through rhinoplasty surgery. Suggesting, therefore, that the distinctive vascularity of the nose and the surrounding area, also the altered tissue anatomy in consequence of the plastic intervention may cause more vascular complications in patients submitted to filler injections in the mentioned facial location.

A case of skin necrosis subsequently of a nose application with HA was described by Chen et al. (2016). During the procedure, it was mentioned that the female patient experienced intense pain and the forehead skin became pale. Unfortunately, the injector did not realize how serious was the situation and released the woman right after applying some massage in the affected area. The patient was admitted to the hospital only 48h later, regarding the intensification of the symptoms. She underwent surgical excision, hyperbaric oxygen therapy, vasodilation medication, antimicrobial treatment, daily local medication to help recovering the skin lesions. Although, after all, roughness in the affected area resulted in deep scars and brow placement asymmetry, which is a very frustrating outcome for someone that was firstly seeking for an enhancement in facial aesthetics. Another similar report was performed by Furtado et al. (2020)

discussing a patient that revealed symptoms of vascular complication in the first day after a nasal HA injection, only being treated after 72 hours with small amounts of hyaluronidase in a single application and some vasodilation medication, that proved being non-effective once the clinical condition evolved. Only 6 days later, the patient started to be successfully treated by another qualified professional as the situation was managed through oral medication including antibiotics, sildenafil citrate, pentoxifylline, also chemical debridement of the affected area and hyperbaric-oxygen therapy. Hyaluronidase treatment should be performed as soon as possible in high doses through intralesional applications. If hyaluronidase is injected within 2 days, full recovery of the skin can be expected. On the contrary, if the application is delayed, there could be an intensified chance of occurring scars and tissue defect formation.

In a research analyzing the treatment after the embolization due to nasal HA injection, Ouyang et al. (2019) noticed that of 35 cases who had vascular occlusive events, 11 presented mild embolization and recovered finely after treatment, having no scars. 19 had moderate embolization, but with no ischemic aggravation or skin necrosis, and 5 had severe episodes leading to longer healing period and scars. Regarding how long it took to happen the embolization, 2 cases were immediate (until 5h after the injection), 28 were early (from 5h to 3 days after the procedure), and 5 were late (more than 3 days after the injection). The treatment of the skin after embolization or vascular occlusion consequently to HA application can be affected by identifying the stage and degree of embolization as soon as possible, and immediately promoting the appropriate management. As happened in the case informed by Cassiano et al. (2020) reporting a skin necrosis following HA application in the forehead, that started with pain, erythema and edema only 2 days after the procedure. The patient was treated less than 24 hours from the onset of symptoms, leaving the incident just a discreet scar.

In certain circumstances, the injecting force may be high enough to push filler particles retrograde towards the brain circulation, afterwards the middle cerebral artery can be occluded when the force recedes, presenting a subsequent cerebral infarction (Shoughy et al., 2019). Cerebral infarction is a very rare condition consequently to HA filler injection, however it was reported by Yang et al. (2020) describing a case in which the patient reached a coma stage only 48h after a nose filling procedure with HA, presenting cerebral infarction, optic nerve edema and ischemia, that soon evolved to gastric ulceration, pulmonary infection, respiratory failure and cerebral herniation, unfortunately dying 6 days after the filling procedure. Preventive measures should be discussed, including the usage of smaller volumes of product, also slow and gentle injection (Parada et al. 2016). However aspiration prior to injection does not ensure vascular safety, it must be performed as observed by Torbeck et al. (2019) in an In Vitro evaluation of pre injection aspiration as a safety checkpoint for HA fillers, concluded that it may have utility as a safety factor, but practitioners may have to adjust the pullback volume and waiting time to visualize the flash, regarding rheological and physiochemical properties. Among the professional injectors, it has been diffused that the use of blunt typed cannulas can help avoiding vascular complications. Nevertheless, Zhou et al. (2020) described that the majority of cases linked to severe HA–related intravascular events referred to their department were performed with cannulas instead of needles, comprising 28 severe cases of injectable HA-caused embolism, of which 25 were done with blunt typed cannulas. These findings suggest that the safety brought by the use of cannulas in HA injections may be overestimated, especially using the ones smaller than 25-Gauge in high-risk zones.

All responsible injectors should have a wide and solid knowledge about facial anatomy and master safe filler injection techniques. Recognition of a vascular incident and start an immediate aggressive treatment is necessary to avoid potentially irreversible complications. To help minimizing adversities the medical history and systemic condition of the patient has to be carefully registered as well as evaluated considering the contraindications: it is mandatory to question about bleeding disorders, systemic diseases, autoimmune affections, allergies, episodes of herpes, formation of keloids, continuous usage of specific medications, pregnancy and breastfeeding, observe the existence of any active infection or inflammatory process and previous cosmetic procedures, once it is not recommended to apply material in the same site where there is already a permanent product, for it can stimulate the creation of nodules or other undesired reactions (Abduljabbar and Basendwh, 2016; Parada et al., 2016; Almeida et al., 2017). The management in possible cases of complications must begin rapidly and be conducted efficiently when observing, above all, intense pain complaints, skin blanching or color changes (livedo, blueish or gray coloration) in the distribution of the regional blood vessels. An additional useful hint is verifying the blood return right after digital compression of the affected area. The return to normal skin color takes no more than 2 seconds; a slower capillary blood return may be a sign of arterial insufficiency and can suggest a vascular occlusion (Habre et al., 2016; Parade et al., 2016).

Bone Reabsorption: Guo et al., (2020) observed an unexpected bone reabsorption in mental region induced by HA fillers. The severity of the bone loss was positively correlated with the injection volume per time, as patients injected with more than 1ml at once showed up as more susceptible to bone erosion compared to the ones that had injected less product. Therefore, these findings raise aware to the administration of large-volume injection of HA dermal fillers.

BDDE Toxicity: A new subject of attention in the topic of HA fillers is the 1,4-Butanediol Diglycidyl Ether (BDDE) that can react with HA under strong base conditions to form stable covalent bonds and is a widely used crosslinking agent in the production of HA filler gels. BDDE is well known for having certain biological toxicity and potential carcinogenicity, being a possible residual agent left in the body after HA applications and probably harmful to the organism in greater concentrations. For that reason BDDE residues of HA gels are currently being widely investigated (Fidalgo et al., 2018; Xue et al., 2020).

Conclusion

The aesthetic benefits and great biocompatibility of the hyaluronic acid-based fillers are widespread; although its misguided usage by incautious professionals, sometimes with no real health interests, became a serious concern due to increasing request for those procedures, and the easy acquisition of the filler products by various injectors that are legally licensed to do such cosmetic treatments, however, without needing to have a certification, formation or even

habilitation on the subject. Hence, in order to reduce the chance of complications it is imperious for a qualified professional to master not only the injection techniques, but also the human anatomy and physiology, the properties of the chosen material and its correct indications to suit each patient. Moreover, it is important to always keep learning and seeking for reliable information, as well being prepared to notice and reverse any possible adversities. Because primarily a health professional has to embrace the non-maleficence principle, having the commitment to do no injury or allow no injury to be inflicted to a patient through neglect, invariably looking for the improvement of their physical and mental health.

REFERENCES

Abduljabbar, M. H. and Basendwh, M. A. 2016. Complications of hyaluronic acid fillers and their managements. *Journal of Dermatology & Dermatologic Surgery*. 20, pp. 100–106

Almeida, A. R. T. and Saliba, A. F. N. 2015. Hyaluronidase in cosmiatry: what should we know? *Surg Cosmet Dermatol*. 73. , pp. 197-204

Almeida, A. T., Banegas, R., Boggio, R., Bravo, B., Braz, A., Casabona, G., Coimbra, D., Espinosa, S. and Martinez, C. 2017. Diagnosis and treatment of hyaluronic acid adverse events: Latin American expert panel consensus recommendations. *Surg Cosmet Dermatol*. 93. , pp. 204-213

Alshaer, Z., Alsaadi, Y. and Mrad, M. A. 2018. Successful Management of Infected Facial Filler with Brucella. *Aesthetic Plastic Surgery*. 42, pp. 1388–1392

Bitterman-Deutsch, O., Kogan, L., and Nasser, F. 2015. Delayed immune mediated adverse effects to hyaluronic acid fillers: report of five cases and review of the literature. Dermatology Reports. 65851. , pp. 12-14

Cassiano, D.; Miyuki T. I., Recio, A. L. and Yarak, S. 2020. . Delayed skin necrosis following hyaluronic acid filler injection: A case report. *J Cosmet Dermatol*. 193. , pp. 582-584

Castro, M. B. and Alcantara, G. A. 2020. . Efeitos adversos no uso do ácido hialurônico injetável em preenchimentos faciais. *Braz. J. Hea. Rev*., 32. , pp.2995- 3005

Chang, S. H., Yousefi, S. and Qin, J. 2016. External compression versus intravascular injection: a mechanistic animal model of filler-induced tissue ischemia. *Ophthal Plast Reconstr Surg*., 324. , pp. 261-266

Chen, Q., Liu, Y. and Fan, D. 2016. Serious Vascular Complications after Nonsurgical Rhinoplasty: A Case Report. *Plast Reconstr Surg Glob Open*. 4, pp. e683

Chung, E., Sim, C. and Hyun Jo, K. 2019. Delayed adverse reactions caused by consecutive injections of different fillers in the same region: Murine skin study. *J Cosmet Laser Ther*., 211. , pp. 33-38

Chung, K. L., Convery, C., Ejikeme, I. and Ghanem, A. M. 2020. A Systematic Review of the Literature of Delayed Inflammatory Reactions After Hyaluronic Acid Filler Injection to Estimate the Incidence of Delayed Type Hypersensitivity Reaction. *Aesthetic Surgery Journal*. 405. , pp. 286–300

Daher, J. C., Silva, S. V., Campos, A. C., Dias, R. C. S., Damasio, A. A. and Costa, R. S. C. 2020. Complicações vasculares dos preenchimentos faciais com ácido hialurônico: confecção de protocolo de prevenção e tratamento. *Rev. Bras. Cir. Plast*., 351. , pp. 02-07

Fan, X, Dong, M., Li, T., Ma, Q., Yin, Y. 2016. Two Cases of Adverse Reactions of Hyaluronic Acid–based Filler Injections. *Plast Reconstr Surg Glob Open*. 4, pp. 01-03

Fidalgo, J., Deglesne, P. A., Arroyo, R., Sepúlveda, L., Ranneva E., and Deprez, P. 2018. Detection of a new reaction by-product in BDDE cross-linked autoclaved hyaluronic acid hydrogels by LC–MS analysis. Medical Devices: Evidence and Research. 11, pp. 367–376

Furtado, G. R., Barbosa, K. L., Tardni, C. D. R., Barbosa, J. R. A. and Barbosa, C. M. R. 2020.

Goodman, G.J., Al-Niaimi, F., McDonald, C., Ciconte, A. and Porter, C. 2020. Why we should be avoiding periorificialmimetic muscles when injecting tissue fillers. *J Cosmet Dermatol*. 19, pp. 1846–1850

Guo, X., Zhao, J., Song, G., Zong, X.,Zhang, D., Lai, C. and Jin, X. 2020. Unexpected Bone Resorption in Mentum Induced by the Soft-Tissue Filler Hyaluronic Acid: A Preliminary Retrospective Cohort Study of Asian Patients. Plastic and ReconstructiveSurgery. 1462. , pp. 147-155

Gutmann, I. E. and Dutra, R. T. 2018. Reações adversas associadas ao uso de preenchedores faciais com ácido hialurônico. Revista Eletrônica Biociências, Biotecnologia e Saúde. 20, pp. 07-17

Habre, S., Nasr, M. W. and Habre, M. 2016. Preenchimento de tecidos moles: nem tão minimamente invasivo. Surgical & Cosmetic Dermatology. 8 2. , pp. 182-183

Hamed-Azzam, S., Burkat, C., Mukari, A., Briscoe D., Joshi, N., Scawn, N., Alon, E. and Hartstein, M. 2020. Filler Migration to the Orbit Shirin. Aesthetic Surgery Journal. Available online at doi.org/10.1093/asj/sjaa264

Horriat, N., Woods, T. R. and Medina, A. 2020. An unusual and delayed complication of hyaluronic acid filler injection: a case report. Case Reports in Plastic Surgery and Hand Surgery. 71. , pp. 68-72

Hu, X. Z., Hu, J. Y., Wu, P. S., Yu, S. B., Kikkawa, D. O. and Lu, W. 2016. Posterior Ciliary Artery Occlusion Caused by Hyaluronic Acid Injections Into the Forehead A Case Report. Medicine. 9511. , pp. 01-03

King, M. 2016. Management of Tyndall effect. Journal of clinical and aesthetic dermatology. 911. , pp. 06-08

Maia, I. E. F. and Salvi, J. O. 2018. O uso do ácido hialurônico na harmonização facial: uma breve revisão. Brazilian Journal of Surgery and Clinical Research. 232. , pp. 135-139

Mansouri, Y. and Goldberg G. 2015. Update on Hyaluronic Acid Fillers for Facial Rejuvenation. Cutis. 96, pp. 85-88

Martin, L. H. C., Hankinson, P. M. and Khurram, S. A. 2019. Beauty is only mucosa deep: a retrospective analysis of oral lumps and bumps caused by cosmetic fillers. British Dental Journal. 227, pp. 281–284

McCraken, M.S., Khan, J.A. and Wulc, A. E. 2016. Hyaluronic acid gel Restylane. filler for facial rhytides: Lessons learned from American Society of Ophthalmic Plastic and Reconstructive Surgery member treatment of 286patients. Ophthal Plast Reconstr Surg. 22, pp. 188-191

Modarressi, A., Nizeta, C. and Lombardi, T. 2020. Granulomas and nongranulomatous nodules after filler injection: Different complications require different treatments. JournalofPlastic, Reconstructive&AestheticSurgery. 7311. , pp.2010 – 2015

Necrose em ponta nasal e lábio superior após rinomodelação com ácido hialurônico – relato de caso. AHOF. 0101. , pp. 62-67

Ouyang, H. W., Li, G. F., Zhu, Yi., Lei, Y.; Gold, . H. and Tan, J. 2019. Treatment of skin soft tissue embolism after

hyaluronic acid injection for injection rhinoplasty in Asian patients. J CosmetDermatol. 183. , pp. 747-754

Parada, M.B, Cazerta, C., Afonso, J. P. J. M. and Nascimento, D. I. S 2016. Overview and management of fillers complications. SurgCosmetDermatol. 84. , pp. 342-351

Pérez, P., Villarroel, A., Andrade, T. and Faba, G. 2019. Reacciónгranulomatosa a cuerpoextrañoenpunta y dorso nasal por materiales de relleno. Presentación de un caso clínico y revisión de la literatura. Rev. Otorrinolaringol. Cir. CabezaCuello. 79, pp. 85-90

Pozuelo, C. C., De Dios, J. D., Mota, X. R. 2020. Multiple oral granulomatous nodules to hyaluronic acid filler. J CosmetDermatol, available online at doi: 10.1111/jocd.13734

Robati, R. M., Moeineddin, F. and Almasi-Nsrabadi, M. 2018. . The Risk of Skin Necrosis Following Hyaluronic Acid Filler Injection in Patients with a History of Cosmetic Rhinoplasty. AestheticSurgeryJournal. 388. , pp. 883-888

Scardovi, S., Goglian, A., Gendra, P. and Gendra, C. 2017. Estudio clínico de eficacia, duración y efectos adversos del implante de Ácido Hialurónicoenel área Buco-Maxilo-Facial. Odontoestomatología. 20 30. , pp. 77-90

Shin, Y. J., An, M. Y., Roh, S. G., Chang, S. C., Lee, N. 2017. Unusual Aspergillus Infection After Dermal Filler Injection. J CraniofacSurg. 288. , pp. 2066-2067

Shoughy, S. S. 2019. Visuallossfollowingcosmetic facial fillerinjection Perda da visão após injeção de preenchimento facial para fins cosméticos. Arq Bras Oftalmol. 826. , pp. 511-513

Sito, G., Manzoni, V. and Sommariva, R. 2019. Vascular Complications after Facial Filler Injection: A Literature Review and Metaanalysis. 126. , pp. 65-72

Torbeck, R. L., Schwarcz, R., Hazan, E., Wang, J. V., Farberg, A. S. and Khorasani, H. 2019. In Vitro Evaluation of Preinjection Aspiration for Hyaluronic Fillers as a Safety Checkpoint. Dermatol Surg. 457. , pp. 954-958

Wang, C., Sun, T., Li, H., Li, Z. and Wang, X. 2020a. Hypersensitivity Caused by Cosmetic Injection: Systematic Review and Case Report. AesthPlast Surg. Available online at doi.org/10.1007/s00266-020-01684-4

Wang, C., Sun, T., Yu, N. and Wang, X. 2020b. Herpes reactivation after the injection of hyaluronic acid dermal filler A case report and review of literature. Medicine. 9924. , pp. e20394

Wortsman, X. 2015. Identification and Complications of Cosmetic Fillers. J Ultrasound Med. 34, pp. 1163–1172

Xue, Y., Chen, H., Xu, C., Yu, D., Xu, H. and Hu, Y. 2020. Synthesis of hyaluronic acid hydrogels by crosslinking the mixture of high-molecular-weight hyaluronic acid and low-molecular-weight hyaluronic acid with 1,4-butanediol diglycidylether.RSC Adv. 10, pp.7206–7213

Yang, H. K. L., Lee, Y., Woo, S. J., Park, K. H., Kim, J. S. and Hwang J.M. 2019. Natural Course of Ophthalmoplegia after Iatrogenic Ophthalmic Artery Occlusion Caused by Cosmetic Filler Injections. PlastReconstr Surg. 1441. , pp. 28-34

Yang, Q., Lu, B., Guo, N., Wang, Y., Ma, X. and Su, Y. 2020. Fatal Cerebral Infarction and Ophthalmic Artery Occlusion after Nasal Augmentation with Hyaluronic Acid—A Case Report and Review of Literature. AesthPlast Surg. 44, pp. 543–548

Yao, B., Shen, F., Zhao, X., Liu, G., and Ding, Y. 2019. Ophthalmic artery occlusion combined with superior sagittal sinus thrombosis caused by hyaluronic acid injection for facial soft tissue augmentation A case report. Medicine. 9836. , pp. e17048

Zhou, S. B., Chiang, C. A. and Liu, K. 2020. False Sense of Safety: Blunt Cannulas Cause the Majority of Severe Vascular Complications in Hyaluronic Acid Injection. Plastic and Reconstructive Surgery. 1462. , pp. 240-241

****