https://dx.doi.org/10.22161/ijaers.72.6 ISSN: 2349-6495(P) | 2456-1908(O)

# The use of hyaluronic acid and polymethylmethacrylate in the skin aging process in a comparative analysis (the advantages, disadvantages and adverse effects of each filler)

Gisele Gonçalves de Carvalho[1], Marilia Fagury Videira Marceliano-Alves[2], Vanessa Hamberger Morett[3], Priscilla Rueles Figueiredo[4], Paula Avelar da Silva Ribeiro Goulart[5], Marco Orsini[6], Adalgiza Moreno[7]

[1] Life Higher Education Institute, Niteroi, Rio de Janeiro, Brazil
[2] Dentistry Research Group, Iguaçu University, Iguaçu University, Nova Iguaçu, Rio de Janeiro, Brazil
[3]Life Higher Education Institute, Niteroi, Rio de Janeiro, Brazil, Email: vanessamorett@gmail.com
[4] Grande Rio University, Duque de Caxias, Rio de Janeiro, Brazil, Rio de Janeiro, Brazil.
[5] Dentistry Research Group, Iguaçu University, Nova Iguaçu, Rio de Janeiro, Brazil
[6] Health and Aging Research Group, Nova Iguaçu, Rio de Janeiro, Brazil
[7] Health and Aging Research Group, Iguaçu University, Nova Iguaçu, Rio de Janeiro, Brazil

***Abstract***— *The dermal fillers are currently a modality of treatment widely sought by those who seek for alternatives to plastic surgery, to delay the signs of aging. These procedures are minimally invasive, capable of attenuating wrinkles and restoring satisfactorily facial volume, although it is imminent the possibility of finding intercurrences related to the use of these materials. The present study aimed to do a bibliographical review regarding two of the dermal fillers frequently used in aesthetic medicine, namely hyaluronic acid and polymethylmethacrylate, respectively classified as biodegradable and non-biodegradable implant materials. Thus, given the particularities of the mentioned products, their general characteristics were described, as well as the comparison and discussion on the framing of these implant materials with regard to: the characteristics considered as ideal in a filler, the annual statistics related to the number of procedures, the number of complications caused by hyaluronic acid and polymethylmethacrylate according to observational clinical studies and the types of adverse effects inherent to the use of each filler studied. According to the developed bibliographical study, it was possible to verify comparatively that although there is no filler that meets all the characteristics considered as ideal, the hyaluronic acid is currently the first choice among implant materials because it presents fewer complications, which can be reversed, unlike polymethylmethacrylate, which is neither a biocompatible nor an absorbable polymer, making it difficult and/or impossible to reverse the complications.*
***Keywords*— *Dermal Fillers. Hyaluronic acid. Polymethacrylate. Complications.***

## I. INTRODUCTION

The aesthetic segment is constantly growing and attracts people who are looking for significant news and results. Historically, the first-choice treatment for facial aging caused by the loss of subcutaneous fat and dermal collagen was the lifting, a surgical treatment in which the spare tissue is removed in an attempt to restore the tone characteristics, promoting a younger appearance. Nowadays, thanks to technological and scientific advances, it is possible to restore the volume of facial contours through minimally invasive aesthetic procedures, offering satisfactory results without the need of a long recovery time [1].The aging process causes considerable dissatisfaction due to the appearance of ridges, depressions in the face, volume loss and bone remodeling. These changes turn the typical convexities of a young individual into an individual with a face that shows concave, flat shapes. This results in a distorted self-image and weakened

*https://dx.doi.org/10.22161/ijaers.72.6* *ISSN: 2349-6495(P) | 2456-1908(O)*

self-esteem, generating frustrations because there is currently an imposition on the part of society, which associates good looks with the sensation of fullness [2]. In this sense, the fillers have been gaining remarkable prominence for presenting excellent results regarding volume restoration, showing great efficacy in reducing expression wrinkles and improving facial contours, contributing to facial harmonization [3].

According to International Society of Aesthetic Plastic Surgery (ISAPS), in 2014, 20 million aesthetic procedures were performed, and Brazil ranked third in the ranking of non-surgical procedures. According to the same research, 51% of the procedures were non-surgical and the most performed were botulinum toxin and skin fillers. ISAPS pointed to botulinum toxin and hyaluronic acid filling as being responsible for 71% of the most non-surgical procedures performed during 2014 [4].Among the main indications of fillings are: restoration of facial contour loss, treatment of furrows and expression lines, harmonization of cheeks and chin, correction of tear through, rhinomodeling, increase of lip volume, increase of volume of the middle third of the face, correction of facial asymmetry and rejuvenation of the hands [5].

The professional should have great knowledge about the materials used in the fillings, which have different origins. Injectables should be safe and have good results with a low complication rate [6]. Currently, Brazil has several options of cosmetic fillers, which are classified according to origin (animal or non-animal), duration (permanent or non-permanent) or according to source (autologous or heterologous). Although these products have a very significant safety margin, between 2003 and 2008, the Food and Drug Administration (FDA) received 930 reports of filler-related adverse effects, of which 823 were classified as severe [7].

There is still no filler considered as ideal, as some materials have disadvantages compared to others, besides the possibility of adverse effects. The only way to exclude the possibility of complications would be using the body's own tissues and this would only be possible through the cultivation of all tissues or from cell differentiation through the stem cells. It is now possible to grow artificial skin, fibroblasts, cartilage cells and stimulate the growth of blood vessels and nerves, but it is not yet possible to reproduce part of organs formed by various interacting cell types, such as the pilosebaceous system, pulmonary alveoli and endocrine glands [6]. In this paper two types of very frequently used fillers nowadays are addressed, being the hyaluronic acid (HA) and the polymethylmethacrylate (PMMA).

The HA is a type of filler classified as biodegradable or non-permanent, of moderate duration, and reabsorbed by the body within 6 to 18 months, depending on the specifications of each manufacturer. PMMA fillers are classified as non-biodegradable and cause a defense reaction in the body, stimulating fibroblasts to produce collagen to be deposited around non-resorbable microspheres, having permanent effects on the tissue where it is applied [5]. Thus, this paper aims to bring a literature review study on the facial fillers based on HA and PMMA, comparing them as to their advantages, disadvantages and possible adverse effects arising from their dermal administration.

## II. LITERATURE REVIEW

### A. *Anatomy*

According to Tamarkin (2004), the skin is basically constituted by two juxtaposed tissues, which are the epidermis and the dermis. Besides these, it is common to observe that some authors consider the stratification of the skin in three distinct layers, including also the hypodermis. The transition between the epidermis and the dermis is named dermoepidermal junction or basement membrane zone [8].The dermis has a mesodermal origin and is about 30 times thicker than the epidermis, and can be divided into two regions: papillary, which is more superficial and reticular, which is deeper [2]. The dermis is constituted by connective tissue, containing elastic fibers, collagen and amorphous fundamental substance, besides containing blood and lymphatic vessels, nerves, cutaneous attachments and erector muscles of the hair. In addition, at this level of the skin, we also find cells such as lymphocytes, plasmocytes, fibroblasts, histiocytes, dendritic cells and mast cells [9].

### B. *Wrinkle formation process and its classifications*

According to Guirro and Guirro (2004), the formation of wrinkles and skin ptosis begins with the loss of the natural elasticity of the integument, due to the reduction of elastic fibers, stiffening of collagen, reduction of connective tissue functions, depletion of tissue oxygenation and decreased of skin turgor. The same authors classify wrinkles as static, dynamic and gravitational. Static wrinkles are visible regardless of muscles movement and arise as a result of repeated movements throughout life, leading to fatigue in the structures that make up the skin [10].

Dynamic wrinkles, also named expression lines, are not perceived in the absence of movement and are due to the repetition of facial mimic muscle movements. Gravitational wrinkles result from facial aging, which

*https://dx.doi.org/10.22161/ijaers.72.6* *ISSN: 2349-6495(P) | 2456-1908(O)*

causes sagging skin, leading to ptosis of facial structures, most notably in the middle third, where the largest number of facial muscle groups is located, tending to suffer more intensely with the gravity action [10].

C.*Skin Fillers*

According to Filho (2006), there is a great demand for skin filling techniques, as they present fast and satisfactory results, with a minimum recovery time in relation to surgical interventions. The same authors mention that the indications of these procedures are directed to the restoration of the anatomical area, due to trauma and scars or signs of aging, treating grooves, superficial and deep wrinkles, depressions, sagging, loss of contour and facial volumization [11]. For Kede and Sabatovich (2015), the choice of filler should be based on the assessment of the degree of aging, age, treatment area, patient expectation, cost, material durability and professional experience with the product [12].

Vargas *et al*. (2009) emphasize that for a filler to be considered as ideal, it must offer the following characteristics: to be biocompatible, to be safe (approved by ANVISA or FDA), to be low cost, to be free of complications, to have good durability, be able to stimulate autologous collagen production, be easy to store, be simple to apply, offer no risk of migration, be free of allergenic testing prior to use and offer no potential to trigger foreign body-type inflammatory reaction. Based on the above characteristics, the ideal filler has not yet been developed [3].

D.*Hyaluronic acid*

Monteiro and Parada (2010) mention that hyaluronic acid (HA) is a polysaccharide that contains between 200 and 100,000 repeated units of D-glucuronic acid and N-acetyl-D-glucosamine disaccharides with molecular weight ranging from 5 (five ) and 6 (six) million Daltons. These authors describe the structure of HA as a straight, unbranched chain composed of disaccharide units, that is, two polyanionic sugar molecules of D-glucuronic acid and N-acetyl glycosamine joined alternately by β 1-4 glycosidic bonds and their repeating dimers are connected by bonds β 1-3 [13].

According to Bonté and Verdier-Sévrain (2007), HA is the main component of the dermis extracellular matrix being synthesized in the fibroblast plasma membrane and released into the extracellular space soon after its production. In addition to the dermal level, this biopolymer is also synthesized in the plasma membrane of synovial, endothelial and muscle cells. The same authors state that the pattern of tissue distribution varies with age, with the total amount of HA reduced over the years. In aged skin we found a reduction in the concentration of this glycosaminoglycan in all layers, except the papillary dermis, which maintains its concentration [14].

Oliveira (2009), HA implants may come from animal origin or from biotechnology. When the origin of the product is animal, it is obtained by extracting the rooster crest or the human umbilical cord and if it comes from biotechnology, it is obtained by bacterial fermentation process. Currently, the most commonly used type is HA of non-animal origin, obtained through culture of nonpathogenic human's bacteria, using *Streptococcus equi* or *Streptococcus zooepidermus*[15].

Antônio *et al*. (2015) point out that hyaluronic acid in vivo has a short half-life, is soluble in water and is degraded by enzymatic action by lysosomes containing hyaluronidases and by reactive oxygen species within just one or two days, which would cause a rapid deterioration of this implant if administered to the skin in its native form [1]. In order for HA to have longer lasting results, this molecule has been chemically modified and stabilized through cross-linking agents, making it less soluble, increasing its resistance and improving its mechanical and biological properties, which increases its half-life and enables its use in biomedical, pharmaceutical and industrial applications [16].

In the cross-linking process, polymeric crosslinking occurs, which is a process that increases and stabilizes the molecule through chemical modifications in the structure of HA, with the formation of cross-covalent bonds in the polymer chains of this biopolymer, involving mainly the carboxylic groups. (-COOH) and / or hydroxyls (-OH) of the backbone. Through these groups occurs the cross-linking between the chains through the addition of substances that can act as facilitators of the reaction [17].

The Food and Drug Administration (FDA) approved the commercialization of HA in 2003 and since then, this filler has gained notoriety because this material has the characteristics that are closest to those considered ideal in a filler because it is safe, easy to apply, non-palpable, non-carcinogenic, non-toxic, biocompatible, biodegradable with good durability in the implanted tissue, has no one or low ability to develop foreign body reaction and it is reversible through the use of hyaluronidase [1].

Dayan and Bassichis (2008) injectable HA is slowly reabsorbed by the tissues there are adjacent to the implant site by isovolumetric degradation. Dayan and Bassichis (2008) mention that the maintenance of volume in the areas where HA is injected is due to the arrival of water at the filling site, as the product reabsorption occurs. This hydration mechanism gives the filled skin a natural

*https://dx.doi.org/10.22161/ijaers.72.6* *ISSN: 2349-6495(P) | 2456-1908(O)*

look and the local turgor is maintained until the product is completely degraded [18].

Crocco *et al*. (2012), reports of adverse events related to HA use are rare, with cases of complications found in less than 2% of the total procedures performed. According to the same authors, complications related to HA fillings may be recent (less than 14 days) or late (between 14 days and 1 year). Among the recent adverse events can be observed: edema, erythema, bruising, infection, telangectasis, nodules and necrosis. Late side effects may include allergic reactions, granulomas and scar hypertrophy [19]. Edema and erythema occur immediately after the procedure and are observed in most cases and tend to regress within a week. They usually occur due to local trauma and increased volume due to the introduction of the product into the skin [5]. Bruises are very common complications and result from vascular injury at the time of the procedure, being more frequent in individuals who take anticoagulants, non-steroidal anti-inflammatory drugs, gingko biloba, vitamin E, among others. These adverse events tend to improve within five to fifteen days [19].

Infections may be viral, bacterial or fungal in origin and are usually related to natural flora, occurring due to inadequate antisepsis, and may also occur by injections into acne sites and contamination of the product used. They have a turgid appearance, accompanied by hyperemia, itching and hypersensitivity [7]. Telangiectasias may arise as a result of tissue trauma caused by skin expansion at the time of injection or excessive local massage of the product [5].

The nodules appear within the first four weeks after the procedure, may be normochromic, whitish or bluish-gray and usually result from the very superficial application of HA or over-application of the product in each area. Necrosis may occur by injection of the product into the lumen of the artery or by arterial compression. Minutes to hours after application, the patient has persistent pain at the filling site and shortly after ischemia and bluish-gray coloration in the filled area. The most at risk areas for necrosis are those that have terminal or superficial blood vessels, such as the glabella, nose, and nasolabial sulcus. However, it is possible to reverse imminent necrosis from vascular compromises associated to the use of injectable HA through the application of hyaluronidase, since this enzyme is capable of cleaving HA reducing the product viscosity, resulting in increased blood supply in the affected region [20].

Allergic reactions to HA products are present in only 0.1% of all procedures performed and are usually due to the presence of bacterial proteins and endotoxins, which may start on the third day after application and last until the sixth month. Reactions are usually local, with edema and flushing, and even more rarely, mild systemic impairment may occur [21].

The granulomas are chronic inflammations and palpable nodular appearance, with modified macrophages and multinucleated cells by histopathological examination. They are perceived between 6 and 24 months after the injection of the product and it is believed that they are not due to hypersensitivity reactions to HA, but caused by reactions associated with the presence of bacterial proteins and endotoxins, resulting from the fermentation process of the product [19]. Hypertrophic scars may appear in cases of HA fill, only at the puncture sites, in patients with a keloid history or formation of hypertrophic scars [19].

E. *Polymethylmethacrylate (PMMA)*

Vieira *et al*. (2006) state that PMMA is a type of thermoplastic acrylic with high physicochemical stability. It is obtained through the polymerization of the methyl methacrylate monomer (MMA), by the addition of polymerization initiators, which are agents capable of forming free radicals upon decomposition. These free radicals are able to capture an electron from the double bonds existing between the carbon atoms of MMA, promoting their breakdown. This process results in a free electron at the carbon atom that has not been reached by the decomposed initiator, which keeps the polymerization from spreading by forming polymer chains formed by the repetition of n monomers [22].

Currently the PMMA has many biomedical applications because it is an inert, transparent and rigid material. Its use in this segment, is present in orthopedics as a bone substitute, in facial maxillofacial surgery as repair tool, in ophthalmology as a basis for intraocular lenses, in neurosurgery and craniofacial repair material, in the manufacture of dentures and other dental materials, such as submucosal esophageal implant for the treatment of gastroesophageal reflux, in prostheses used in cosmetic surgery, in radiology as a radiation shield, in the manufacture of ortheses directed to podology, among other applications [23].

As Avè and Avè (2015) mention, PMMA is an inert and biocompatible polymer and can therefore be applied as a skin implant. For this material to be used for dermal filler purposes, it must be presented as smooth and homogeneous microspheres with a diameter ranging from 20 to 80 µm and must be in suspension in a vehicle for injection of the product to be possible [24].

According to Yamaguchi (2017), this substance has been used as a skin implant since 1989, to fill deep wrinkles and grooves, to treat acne scars and to define the

https://dx.doi.org/10.22161/ijaers.72.6 ISSN: 2349-6495(P) | 2456-1908(O)

facial contour. This author mentions that PMMA microspheres are not biodegradable and therefore induce an inflammatory and fibrotic reaction around them, involving the arrival of monocytes, histiocytes and fibroblasts. At the histological level, neutrophils are observed in the first 24 hours after injection and within three days after application, there is a predominance of monocytes, which quickly differentiate into macrophages to try to phagocyte the microspheres. From the sixth to the ninth day after implantation, fibroblasts surround all microspheres, increasing collagen synthesis. Two to three months after filling, the increase in tissue density due to collagen production from the fibroblasts surrounding the microspheres becomes relevant. After four months, there is no more fibrotic reaction present, but the fibrous tissue around the microspheres is able to permanently stimulate the production of collagen fibers [25]. Regarding complications related to the use of this material, Costa *et al*. (2015) describe a low rate of adverse effects related to the use of PMMA, ranging from 0.01% to 3% of the total procedures performed [26].

Although PMMA is considered a safe filler, complications related to host immunology can occur due to the fact that it is a non-biodegradable polymer [27], which in many cases has permanent and hard to treat damages [28] In the first 72 hours after injection, some reactions such as edema, erythema, bruise and allergies are expected. In addition to immediate onset reactions, PMMA filling may also cause persistent edema, erythema and pruritus, infections, local pigmentation changes, telangiectasias, nodule formation, foreign body granulomatous reaction, necrosis, material migration, material extrusion and scars [29]. Since edema and erythema are early onset reactions related to local trauma, these complications usually disappear within a few days. If erythema persists, it may be indicative of technical mistakes resulting from injections in very surface planes [24]. Bruises are adverse effects resulting from vascular injury, often caused using needles during the technique. These vascular injuries can be prevented using microcannulas in place of needles [3].

Allergy cases may result from the administration of Artefill® (commercial presentation of PMMA), due to the presence of bovine collagen in its vehicle, which may cause hypersensitivity reactions, being recommended, therefore, the skin test of sensitivity before the implant injection [27]. Infections are adverse events inherent to any invasive procedure and may occur when antisepsis is inadequate. Although infections can be viral, fungal or bacterial origin, the latter is the most common cause and the most found pathogens are those that make up the resident flora [7]. The change of the local pigmentation may be due to hemosiderin accumulation or may result from the inflammatory process, causing post inflammatory pigmentation, being a complication observed mainly in the higher skin phototypes, such as phototypes IV and V [3].

Days or weeks after the procedure, telangiectasis may appear, which are new capillaries, arterioles and venules at the implant site. The appearance of these new vessels is due to local trauma during the filling and expansion of the skin by the applied product [5]. Necrosis cases associated with the fillings occur by intravascular injection or compression of the blood vessel by the implanted product, resulting in vascular occlusion and preventing the flow of blood. Although this complication is inherent to any kind of filler, PMMA is more likely to generate permanent complications, since there are no measures to be adopted for reversal of the clinical picture when this polymer is used [5].

Avè and Avè (2015) point out that nodule formation may result from the quality of the filler (microspheres with irregularities and / or impurities) or from the technical error by the professional (very superficial application, overcorrection or application in very deep planes) [24]. Funt and Pavicic (2013) classify the nodules as noninflammatory or inflammatory. The first evolve with absence of inflammatory process, can be visible, are well defined and do not increase in volume. Inflammatory nodules develop edema, erythema and hypersensitivity, which may be due to hypersensitivity reactions to the implant material or may result from the formation of biofilms, which consist of an agglomerate of filling material surrounded by negative culture bacteria that secrete virulence factors, making them resistant to antibiotics [5].

Foreign body granulomas present as persistent inflammatory nodules, accompanied by reddish plaques and papules with negative culture. It is a defense reaction of the organism in which activated macrophages secreting inflammatory cytokines, surround PMMA microspheres, to prevent migration of the material [5]. Migration of PMMA microspheres may occur by hematogenous, lymphatic or can be by phagocytosis mediated by macrophages. Hematogenous propagation occurs when intravascular injection of the material is performed, being the pulmonary capillaries the most probable destination of the microspheres. Lymphatic propagation occurs when injection is performed into larger caliber lymphatic vessels, being the lungs and local lymph nodes, the most likely destination of the microspheres. In phagocytosis mediated by macrophages, these cells transport phagocytic

https://dx.doi.org/10.22161/ijaers.72.6 ISSN: 2349-6495(P) | 2456-1908(O)

microspheres from the implant site to the local lymph nodes [30].

PMMA particles may migrate from the implant site or may extrude the material due to a granulomatous inflammatory response. In these cases, appropriate drug treatment should be adopted and if there is no satisfactory response, surgical removal should be performed. Both material extrusion and surgical excision can lead to unsightly scarring [28].

## III. RESULTS AND DISCUSSION

Based on scientific evidences, this paper presents below, comparative tables between HA and PMMA, showing the advantages and disadvantages of each filler regarding their peculiarities, as well as the statistical parameters presented in the mentioned literature.Although there is still no filler material that meets all the characteristics considered as ideal in a filler [11], HA compared to PMMA has greater advantages because it is safe (approved by ANVISA or FDA), biocompatible, simple to use, easy storage, does not offer risks of material migration, is free of allergenic tests prior to use and does not offer risks of foreign-body granulomatous reaction (TABLE I).

*Table I: Comparison between HA and PMMA regarding the characteristics considered as ideal in the skin filler materials.*

| IDEAL CHARACTERISTICS | HA | PMMA |
|---|---|---|
| Safe | YES | YES |
| Biocompatible | YES | YES |
| Simple application | YES | NO |
| Low cost | NO | YES |
| Good durability | NO | YES |
| Free of complications | NO | NO |
| Easy storage | YES | YES |
| No migration risk | YES | NO |
| Stimulation of collagen production | NO | YES |
| Free from allergenic tests prior to use | YES | NO |
| No risk of foreign body inflammation | YES | NO |

Source: Adapted from Vargas et al. (2009).

The analysis of the table above allows us to state that HA reaches most of the criteria considered as ideal in a filler, especially regarding to safety criteria, which is the probable reason why this implant has been occupying the first position in the ranking of the most used fillers worldwide. In addition, the number of HA implants performed annually is progressively increasing, contrary to what is observed with PMMA implants, which presents oscillations in the number of procedures performed between 2011 and 2018, according to annual statistical surveys published by American Society of Plastic Surgeons (ASPS) (TABLE II).

*Table II: Comparison between HA and PMMA regarding the number of procedures performed by plastic surgeons, from 2011 to 2018.*

| YEAR (ASPS) | HA | PMMA |
|---|---|---|
| 2011 | 1,303,656 | 16,836 |
| 2012 | 1,423,136 | 18,342 |
| 2013 | 1,675,601 | 17,317 |
| 2014 | 1,802,247 | 17,344 |
| 2015 | 1,951,692 | 18,051 |
| 2016 | 2,012,672 | 17,345 |
| 2017 | 2,091,476 | 17,639 |
| 2018 | 2,128,923 | 17,564 |

Available at: https://www.plasticsurgery.org/news/plastic-surgery-statistics?sub=2007+plastic+surgery+statistics

Several clinical studies (TABLE III) point out the complications caused using HA and PMMA skin fillers. Friedman *et al*. (2002) carried out a worldwide survey about the adverse effects caused by non-animal HA fillers and observed 144 complications out of a total of 262,000 procedures performed during the year 2000 [31]. André (2004) evaluated the non-animal HA security degree in a five-year study (from 1997 to 2001), including 4,320 patients. Of this total, 34 complications were observed, being 16 of this total related to immediate hypersensitivity reactions and the other 18 were due to delayed onset adverse reactions [32]. Morris *et al*. (2008) conducted a retrospective study of 145 patients who underwent HA implants in the face. From this total, 6 cases of complications were observed, including: edema (2 cases), vagal vessel reaction during injection (1 case), bruising (2 cases) and herpes simplex virus (1 case). (33)

Bagal *et al*. (2007) observed a group of 72 patients who underwent PMMA facial implants in order to conduct a satisfaction survey about the procedure. However, only 40 individuals returned for reevaluation and only these patients answered to the survey, which revealed 5 cases of complications related to the facial filling, as well as other data inherent to the study [34]. Zielke *et al*. (2008) analyzed 56 patients treated with PMMA and identified 6 cases of complications and the granulomatous reaction was the most prevalent adverse reaction [35-36]. Carpaneda and Carpaneda (2012) accompanied 63 individuals who underwent PMMA

*https://dx.doi.org/10.22161/ijaers.72.6* *ISSN: 2349-6495(P) | 2456-1908(O)*

fillings and identified 58 complications, most of them related to late onset adverse effects [36-37].

*Table III: Number of complications related to the use of HA and PMMA fillers according to observational clinical studies.*

| RESEARCH | FILLER | NUMBER OF PATIENTS | NUMBER OF COMPLICATIONS |
|---|---|---|---|
| Friedman *et al.*, 2002 [31] | HA | 262.000 | 144 |
| André, 2004 | HA | 4.320 | 34 |
| Morris *et al.*, 2008 [32] | HA | 145 | 6 |
| Bagal *et al.*, 2007 [34] | PMMA | 40 | 5 |
| Zielke *et al.*, 2008 [35] | PMMA | 56 | 6 |
| Carpaneda and Carpaneda, 2012 [37] | PMMA | 63 | 58 |

In a percentage analysis of the results obtained in the mentioned researches, it was found in the studies in which HA was used as an implant, a complication rate of 0.05%, 0.7% and 4.1%, respectively, according to the chronological order of publications. In studies using PMMA as an implant, the complication rate was 12.5%, 10.7% and 92%, respectively, according to the chronological order presented. The observation of these data shows a lower frequency of complications related to the use of HA when compared to the use of PMMA. Although the literature indicates a low rate of adverse events related to the use of HA and PMMA fillers, several types of complications may arise due to the use of both skin implants. However, besides being able to present all the complications that are likely to occur with HA, the PMMA can also generate adverse events that are not observed with the use of HA, as shown in TABLE IV [19; 26].

As stated in the table above, most complications can happen to both HA and PMMA. However, some of these common reactions occur more frequently when using PMMA because it is a non-biodegradable substance [11]. Edema, erythema and bruise are adverse events that frequently occur upon the implantation of any filler material, since they are complications resulting from the inflammatory process and possible vascular injuries caused by mechanical trauma [12]. Infections are adverse events that can occur in any filling technique because they are usually caused by improper antisepsis at the injection site, using non-sterile materials during the procedure, or by product contamination [5]. Allergic reactions related to HA fillings have become less and less frequent since this glycosaminoglycan began to be obtained primarily by bacterial fermentation through a laborious purification process [38]. In PMMA fillers, the rates of allergic reactions are more significant, since there is a wide use of products containing bovine collagen, which commonly provide allergic conditions because it is a non-biocompatible component [27].

*Table IV: Types of adverse reactions related to the use of HA and PMMA fillers.*

| ADVERSE REACTIONS | HA | PMMA |
|---|---|---|
| Edema | YES | YES |
| Erythema | YES | YES |
| Bruise | YES | YES |
| Infection | YES | YES |
| Allergic reactions | *YES | YES |
| Telangiectasias | YES | YES |
| Hypertrophic scar | *YES | YES |
| Changes in local pigmentation | *YES | YES |
| Nodules | *YES | YES |
| Granulomas | *YES | YES |
| Necrosis | YES | YES |
| Foreign body granulomas | NON-OCCURRENCE | YES |
| Material migration | NON-OCCURRENCE | YES |
| Material extrusion | NON-OCCURRENCE | YES |
| Surgical excision | NON-OCCURRENCE | YES |

Legend: * = rare event (when compared to the frequency of the same complications arising from PMMA use). [19; 29].

Telangiectasias may occur by the introduction of any filler material, since the formation of new vessels is due to the stretching of the skin due to the volume offered or by vigorous massage at the site of the procedure. [5]. During the remodeling phase of healing process, the levels of inflammatory cells, fibroblasts, and blood vessels at the affected site tend to emigrate or undergo apoptosis, ending healing. In cases of persistent inflammatory process, with consequent maintenance of increased cellularity, the

https://dx.doi.org/10.22161/ijaers.72.6 ISSN: 2349-6495(P) | 2456-1908(O)

formation of hypertrophic or keloid scars is observed [39]. As PMMA fillers commonly generate a much more intense and prolonged inflammatory process compared to HA implants, there is a higher incidence of hypertrophic scars in individuals undergoing PMMA treatment, despite being a complication that is likely to occur with both substances when the individual is prone to keloid formation [19].

The change in color at the procedure site may occur with both PMMA and HA, being a rare event in HA fillings because it is due to a technical error, from the very superficial application of the product, which can cause a whitish or bluish-gray hue on the skin by the Tyndall effect [19]. In contrast, PMMA fillers may produce more often hyperpigmentation resulting from hemosiderin accumulation, due to an exacerbated and prolonged inflammatory process, which commonly occurs with this filler, causing post inflammatory pigmentation [3].The nodules resulting from HA implants are not usually inflammatory and are associated with technical errors, when the professional injects the product very superficially or when there is excess of material in a certain area [19].The nodules resulting from PMMA fillers can also result from a very superficial application of the product or may be from poor material quality, when there are irregularities on the microspheres or when there are impurities attached to the polymer particles [24]. As PMMA is a non-absorbable material, these nodules can develop inflammation, caused by hypersensitivity reactions to the implant or by the formation of biofilms around the microspheres [5].

Granulomas consist of palpable and nodular chronic inflammations, presenting modified macrophages and multinucleated cells on anatomopathological examination [19]. As the nodules, granulomas may be due to superficial injections, excessive application of the material or may be caused by irregularities and / or impurities on the surface of the injected particles. These complications are most commonly found in long term fillers such as PMMA but may also occur in rare cases when HA fillers are used [24]. Regarding HA, it is believed that granulomas are not caused by the glycosaminoglycan hypersensitivity reactions, but by reactions associated with the presence of bacterial proteins and endotoxins resulting from the fermentation process of the product [19]. The cases of necrosis associated with fillings occur by intravascular injection or compression of the blood vessel by the product, resulting in vascular occlusion and preventing the flow of blood. Although this adverse reaction is inherent to any type of filler, PMMA is more likely to generate permanent complications, since there are no conducts to be adopted to reverse the picture when this polymer is used [5].When the HA is the responsible material of vascular occlusion, it is possible to reverse the condition using high doses of hyaluronidase at the first signs of necrosis [20].

Foreign body granulomas do not occur with the use of HA. It is a defense reaction of the organism in which activated macrophages secreting inflammatory cytokines surround the PMMA microspheres in an attempt to prevent the material migration, forming persistent inflammatory nodules, accompanied by negative culture reddish plaques and papules [5].The migration of PMMA microspheres can occur through the blood, when intravascular injection of the material is performed, via the lymphatic system, when the filler is injected into thicker lymphatic vessels or by phagocytosis measured by macrophages, when these cells carry the microsphere [30].

The studied literature does not indicate the HA migration because it is a biocompatible and absorbable material. Regarding PMMA, several experimental studies, such as McLelland *et al*. (1997) and Capella *et al*. (1999), reported evidences of PMMA particles migration in the analyzed histological sections [42].PMMA extrusion may occur when injection is performed in superficial planes (within or near the papillary dermis), which leads to ischemia due to increased tension at the implant site by the rigidity of the microspheres added to granulomatous inflammatory response. Complications at this level require immediate surgical excision due to the risk of secondary bacterial infection, or even mycobacterial infection [43].

## IV. CONCLUSION

The aging process leads to the appearance of wrinkles, loss of volume and loss of facial contour. Seeking to improve these tissue changes, there is a significant increase in the demand for dermal filling procedures every year, aiming for a naturally younger looking face. However, by the variety of fillers currently available on the market, among them, the hyaluronic acid and the polymethylmethacrylate, before choosing one or the other implant material, it is necessary to carefully observe each patient's profile, regarding the objectives, indications, contraindications, advantages and disadvantages, and the potential for imminent complications with each filler.

Polymethylmethacrylate is among the most intercurrent filling materials, as it is a permanent polymer, which makes it difficult or impossible to reverse complications when they occur. In addition, the corrections offered by PMMA are long lasting but not lifelong, as this material remains static while the overlying dermis continues to suffer the dynamic changes inherent in

*https://dx.doi.org/10.22161/ijaers.72.6* *ISSN: 2349-6495(P) | 2456-1908(O)*

aging. The literature review presented in this paper allows us to state that although there is no filling material free of complications, hyaluronic acid is currently the main choice among implants, as it is an absorbable material and provide satisfactory results with a minimum number of complications, which can be reversed.

## V. ACKNOWLEDGMENT

First thank God for giving me health and strength to reach my goals and make all dreams come true.To my spouse, Felipe for the encouragement, companionship and patience demonstrated throughout this course.To my mother, Mari Helena, for always being present in my life encouraging each step to be taken and extending her hands, showing at all times, unconditional support and infinite love.To our friends who were part of this walk.To our teachers for contributing to our learning throughout the course.

## REFERENCES

[1] Antônio C. R., Antônio J. R., Coura M. G. G., David E. F., Alves F. T., Rollemberg I. Microcânulas em dermatologia: especificações. Surgical and Cosmetic Dermatology 07: 241-244, 2015.

[2] Audino M. C. F., Schmitz A. Cirurgia plástica e envelhecimento. Revista Brasileira de Ciências do Envelhecimento Humano 09: 21-26, 2012.

[3] Vargas A. F., Amorim N. G., Pitanguy I. Complicações tardias dos preenchimentos permanentes. Revista Brasileira de Cirurgia Plástica 24: 71- 81, 2009.

[4] International Society of Aesthetic Plastic Surgery, 2015. Available in: <http://www.isaps.org/media/default/global-statistics/2015ISAPSResults.2015.pdf>. Acesso em: 22/03/2018.

[5] Funt D., Pavicic T. Dermal fillers in aesthetics: an overview of adverse events and treatment approaches. Clinical, Cosmetic and Investigational Dermatology 06: 295-316, 2013.

[6] Maio M. Tratado de Medicina Estética. 2ª ed., Ed. Roca, São Paulo, 2017.

[7] Parada M. B., Cazerta C., Afonso J. P. J. M., Nascimento D. I. S. Manejo de complicações de preenchedores dérmicos. Surgical and Cosmetic Dermatology 08: 342-351, 2016.

[8] Tamarkin D. Uso da Iontoforese para Aumento da Permeação de Cosméticos. Cosmetics & Toiletries 6: 76- 82, 2004.

[9] Nelson D. L., Cox M. M. L. Princípios de Bioquímica. 4ª ed., Ed. Sarvier, São Paulo, 2006.

[10] Guirro E., Guirro R. Fisioterapia dermato- funcional. 3ª ed., Ed. Manole, São Paulo, 2004.

[11] Filho J. O. Preenchimento cutâneo. In Azulay, R., Azulay, D. Dermatologia. 4ª ed., Ed. Guanabara Koogan, Rio de Janeiro, 2006: 1131- 1135.

[12] Kede M. P. V., Sabatovich O. Considerações gerais: técnicas de preenchimento, áreas de risco e complicações. In: Sabatovich, O., Kede, M. P. V. Dermatologia Estética. 3ª ed., Ed. Atheneu, Rio de Janeiro, 2015: 661- 673.

[13] Monteiro E. O., Parada M, O. B. Preenchimentos faciais – parte um. Revista Brasileira de Medicina 67: 6-14, 2010.

[14] Bonté F., Verdier- Sévrain S. Skin hydration: a review on its molecular mechanisms. Journal Cosmetic Dermatology 06: 75-82, 2007.

[15] Oliveira A. Z. M. Desenvolvimento de formulações cosméticas com ácido hialurônico. 2009. Dissertação (Mestrado em Tecnologia Farmacêutica). Faculdade de Farmácia Universidade do Porto, Porto, Portugal, 2009.

[16] Tomihata K., Ikada Y. Crosslinking of hyaluronic acid with water- solublecarbodiimide. Journal of Biomedical Materials Research 37: 243-251, 1997.

[17] Souza V. F. Preparação e caracterização de micro e nanopartículas de ácido hialurônico com encapsulação do extrato bruto vegetal da arrabidaea chica (humb. & bonpl.) verlot para aplicações farmacêuticas e cosméticas. 2012. Tese (Doutorado em Engenharia Química, na área de concentração de Processos Biotecnológicos). Faculdade de Engenharia Química da Universidade Estadual de Campinas, Campinas, 2012.

[18] Dayan H., Bassichis B. A. Facial dermal fillers: selection of appropriate products and techniques. Aesthetics Surgery Journal 28: 335- 347, 2008.

[19] Crocco E. I., Alves R. O., Alessi C. Eventos adversos do ácido hialurônico injetável. Surgical and Cosmetic Dermatology 04: 259- 263, 2012.

[20] Cohen J. L. et al. Treatment of hyaluronic acid filler- induced impending necrosis with hyaluronidase: consensus recommendations. Aesthetic Surgery Journal 35: 844-849, 2015.

[21] Maio M., Oliveira L. G. L. Complicações nos procedimentos de inclusão. In Maio, Maurício de (editor). Tratado de Medicina Estética. 2ª ed., Ed. Roca, São Paulo, 2017: 1064-1068.

[22] Vieira A., Sossai K., Micaela R., Tonon M., Vescovi V., Valle R. Polimetilmetacrilato. Revista Educação e Tecnologia, 2006. Disponível em: <http://www.faacz.com.br/revistaeletronica/links/edicoes/2006_02/edutec_aquila_polimetilmetacrilato_2006_2.pdf>. Acesso em: 10/06/2018.

[23] Gonçalves G. A. B. Nanocompósitos de PMMA/ HA/ Grafeno para aplicações biomédicas. Tese (Doutorado em Engenharia Mecânica)- Departamento de Engenharia Mecânica, Universidade de Aveiro, Portugal, 2012.

[24] Avè B. R. C., Avè P. R. C. PMMA e Etilmetacrilato. In Sabatovich, O., Kede, M. P. V. Dermatologia Estética. 3ª ed., Ed. Atheneu, Rio de Janeiro, 2015: 745- 753.

[25] Yamaguchi C. Substâncias não biodegradáveis. In Maio, Maurício de (editor). Tratado de Medicina Estética. 2ª ed., Ed. Roca, São Paulo, 2017: 1021- 1033.

[26] Costa V. D. T. et al. Reação nodular ao preenchedor e neuralgia do trigêmeo ipsilateral: acaso ou novo efeito colateral ao preenchedor permanente? Revista Surgical and Cosmetic Dermatology 07: 39-42, 2015.

[27] Lemperle G., de Fazio S., Nicolau P. ArteFill: a third-generation permanent dermal filler and tissue stimulator. Clinics in Plastic Surgery 33: 551-65, 2006.
[28] Loda G., Papaiordanou F., Filho J. J. T. M., Bravo B. S. F., Abreu L., Cuzzi T. Tratamento cirúrgico seriado de múltiplos granulomas por PMMA. Surgical Cosmetic Dermatology 08: 366- 369, 2016.
[29] Lemperle G., Morhenn V., Charrier U. Human histology and persistence of various injectable filler substances for soft tissue augmentation. Aesthetic Plastic Surgery 27: 354-366, 2003.
[30] Lemperle G, Rullan P. P., Gauthier- Hazan N. Avoiding and treating dermal filler complications. Plastic Reconstructive Surgery 118: 92-107, 2006.
[31] Friedman P. M., Mafong E. A., Kauvar A. N., Geronemus R. G. Safety data of injectable nonanimal stabilized hyaluronic acid gel for soft tissue augmentation. Dermatology Surgery 28: 491-494, 2002.
[32] André P. Evaluation of the safety of a nonamimal stabilized hyaluronic acid (NASHA-Q-Medical, Sweden) in European countries: a retrospective study from 1997 to 2001. Journal of the European Academy of Dermatology Venereology 18: 422-425, 2004.
[33] Morris C. L., Stinnett S. S., Woodward J. A. Patient-preferred sites of Restylane injection in periocular and facial soft- tissue augmentation. Ophthalmic Plastic and Reconstructive Surgery 24: 117-121, 2008.
[34] Bagal A., Dahiya R., Tsai V., Adamson P.A. Clinical experience with polymethylmethacrylate microspheres (Artecoll) for soft-tissue augmentation: a retrospective review. Archives of Facial Plastic Surgery 09: 275-280, 2007.
[35] Zielke H., Wölber L., Wiest L., Rzany B. Risk Profiles of different injectable fillers: results from the injectable filler safety study (IFS Study). Dermatologic Surgery 34: 326-335, 2008.
[36] Limongi R. M., Tao J., Borba A., Pereira F., Pimentel A. R., Akaishi P., Cruz A. A. V. Complications and management of polymethylmethacrylate (PMMA) injections to the midface. Aesthetic Surgery Journal 36: 132–135, 2016.
[37] Carpaneda E. M., Carpaneda C. A. Adverse results with PMMA fillers. Aesthetic Plastic Surgery 36: 955-963, 2012.
[38] Chong B. F., Blank L. M., Mclaughlin R., Nielsen L. K. Microbial hyaluronic acid production. Applied Microbiology and Biotechnology 66: 341- 351, 2005.
[39] Mendonça R. J., Coutinho- Netto J. Aspectos celulares da cicatrização. Anais Brasileiros de Dermatologia 84: 257-262, 2009.
[40] McClelland M., Egbert B., Hanko V., Berg R. A., DeLustro F. Evaluation of artecoll polymethylmethacrylate implant for soft-tissue augmentation: biocompatibility and chemical characterization. Plastic Reconstructive Surgery 100:1466-1474, 1997.
[41] Capella N. M. Aplicação de polimetilmetacrilato em prega vocal de cão. XXIII Congresso Brasileiro de Cirurgia. Rio de Janeiro, Brasil, 1999.
[42] Herdt M. A. Possível migração e análise histopatológica de injeções de polimetilmetacrilato em ratos Wistar. Graduação em Medicina - Universidade Federal de Santa Catarina, Florianópolis, 2007.
[43] Fischdick H. A., Amorim N. F. G. Caracterização e tratamento cirúrgico das complicações após injeção de PMMA na face. Revista Oficial do Instituto Ivo Pitanguy e Associação de ex- alunos do Professor Ivo Pitanguy 174, 2016.