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Review

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Complications following permanent fillers use: A review of causative agents, pathology and treatment options

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Abstract

Introduction

The treatment of facial aging features has led to the development of several skin fillers over the past few years. Today, dermal fillers are commonly subdivided on the basis of by their turnover in the skin in temporary, semi-permanent, and permanent.

Permanent fillers may be identified by their morphological aspects. There are a number of permanent fillers each of them with its own strengths, drawbacks, and indications. Patients and clinicians desire both a safe product and a durable correction. However, an inflammatory and fibrotic reaction is developed at their contact, depending on the nature of the product and the patient.

This review relates to the morphological aspect of permanent fillers (Polymethylmethacrylate, Polymethylmethacrylate plus hyaluronic acid, Polydimethyl-siloxane, Polyacrylamide Gel, Alkylamides, and Silicone), the normal tissue reaction after injection, and more frequently observed side effects.

Conclusion

They mainly complications following permanent fillers use consist of granulomatous reactions with inflammatory nodules which may appear long after injection. So, the suggestion is to use a temporary injectable product to minimize the inconvenience and cost of permanent fillers injections.

Introduction

Once it has been decided that soft tissue augmentation is to take place the choice of the filling substance to be used is the most important one. The treatment of facial aging features has led to the development of several skin fillers over the past few years. These fillers include autologous fat [1,2,3] bovine serum collagen,[4,5,6,7] autologous and allogeneic human collagen and expanded polytetra-fluoroethylene.[8]

Then, hyaluronic acid fillers have been proposed as alternatives to other temporary skin fillers for treating facial skin lines and for providing lip augmentation.[9,10]

Today, dermal fillers are commonly subdivided on the basis of by their turnover in the skin in temporary, semi-permanent, (duration is often longer than 18 months but the exact time frame is variable), and permanent.

Permanent fillers may be identified by their morphological aspects. There are a number of permanent fillers each of them with its own strengths, drawbacks, and indications. Patients and clinicians desire both a safe product and a durable correction. However, an inflammatory and fibrotic reaction is developed at their contact, depending on the nature of the product and the patient. The aim of this review is to present an update of the complications following permanent fillers use: causative agents, pathology and treatment options are described.

Discussion

Polymethylmethacrylate (PMMA)

One of the most common fillers is PMMA. It is a permanent injectable soft tissue filler, a "mixed implant" with a biphasic nature; it is composed of a solid phase made up of polymethylmethacrylate (PMMA) microspheres with a smooth surface (25%) suspended in a partially denatured bovine collagen (75%) solution used as a carrier gel. The absence of the immunogenic telopeptides adds a less antigenic character to the collagen molecule.[11,12]

Ideal patients are those with wrinkles and well-defined folds, acne scars, contour increases, and defects of soft tissues of similar size to the face and other areas with little excess skin. It is injected subdermally with a constant pressure throughout the injection. After the injection, the implant must be massaged to eliminate possible bumps and ensure equal distribution. The patient must avoid muscular mimic movements during the first days after the injection.[11]

Gradually, during one to three months after injection, the component of 80% collagen contained in this filler is degraded and is replaced by granulomatous reaction embedded within collagen bundles. The fibrous conjunctive tissue then replaces the volume of the vehicle formed by collagen during the first four months producing a long-lasting augmentation. However, during the first six months the implant changes before the final result is apparent. So, ideally, two to four injections with a one month interval are necessary. At present, the longest duration described in literature is ten years.[12]

Allergic reactions with the collagen component are rare. However, skin tests are necessary. Moreover, people presenting with atrophic affections of the skin and autoimmune diseases should not be injected with this product.[11,12]

Frequent acute adverse effects include redness, swelling, and pain (usually within two days after injection). Bruises are rare but can last up to one week, and itching may appear during the first months. Other technical adverse effects include unequal distribution of an excessive amount of filling product or accidental displacement due to a marked expression of the face; small

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veins also can appear on thin skin.[11] The clinical complications, where histological analysis was performed, consist of induration and nodules appearing 3 to 24 months after injection. Pollack claims that most of the complications relate to a too-superficial injection.[13] Lemperle et al.[14,15] propose that the varying degree of inflammatory reaction and fibrosis inflammatory led to granuloma and the hypertrophic scarring. The treatment of choice is a series of intralesional corticoid injections. Steroids function by inhibiting the activity of fibroblasts and macrophages, therefore preventing collagen deposit and the formation of giant cells. Certain side effects and late complications of this filler[14,15] forced the manufacturer in the United States to make radical changes and a new formulation.

Polyethylmethacrylate plus hyaluronic acid (PMMA+HA)

There are other products based on PMMA which are composed of two phases of non-animal origin: a liquid vehicle and a solid phase for 60% and 40% of volumes, respectively. The liquid vehicle consists in a hyaluronic acid (HA) produced by Streptococcus equi in a bacterial fermentation and later purified for its use. HA is non-allergenic. The solid phase of the implant is the acrylic hydrogel, copolymer of hydroxymethacrylate (HEMA) and ethylmethacrylate, (EEMA), largely used and well tolerated in other medical applications. In this product, the acrylic hydrogel particles are larger for injections into the deeper layers of the dermis, at the junction between the dermis and the hypodermis, whereas in another formulation, particles are smaller because the product is injected less deeply into the sub-periosteal layer or the hypodermis. Hydrogel particles are smooth walled, acting as a scaffold for collagen fibres to form a loose network around the particles that should remain in place after the hyaluronic gel reabsorption because of the neo-collagen development.[15,16] Patients generally require two to three injections three months apart to allow the implant and the fibrotic reaction to stabilize. Short-term adverse effects are pain after the injection, itching, discoloration, sensitivity to touch, palpable bumps, redness, and oedema. Long-range side effects appear on average six months after injection, consisting of indurations, nodules, swelling, and sometimes redness at the point of injection. Serious complications such as granulomas were initially estimated at less than 1 per 15,000 treatments.[16] They are treated by intralesional injection of corticoids.

Contraindicated sites include the mucous part of the lips, the periorbital zones, horizontal lines on the forehead, and perioral wrinkles. Patients with previous history of hypertrophic scar, autoimmune or inflammatory diseases, multiple allergies, and known allergy to sodium hyaluronate or hyaluronic acid should not be injected.[11,12]

These fillers are considered semi-permanent implants. Although the body absorbs the vehicle made of hyaluronic gel in one or four months, the non-biodegradable acrylic hydrogel particles remain in place for more than 12 months and induce a tissue response to yield long-lasting results.

Polydimethylsiloxane plus polyvinylpyrridolone (PDMS + PVPD)

PDMS is another filler which is a biphasic and permanent soft tissue implant. It consists of 38% textured polydimethylsiloxane (silicone) particles in suspension in a 62% polyvinylpyrrolidone gel carrier. The biocompatible gel vehicle is a water-soluble homo-polymer and the solid phase of the implant is a non-biodegradable inert substance. The silicone particles are spheroid in order to prevent migration toward the lymphatic ganglia or other parts of the body, as well as phagocytosis by macrophages directed against foreign bodies. Moreover, the use of structured particles reduces rigidity and contracture of scar tissue by improving the symmetry of collagen formation around the particle.[11,12]. It is important not to inject this filler too superficially but in the sub-dermic level at the dermis-hypodermis junction slowly in a withdrawal manner through a cannula along previously formed channels. During the injection the gel behaves as a lubricant to suspend the silicone particles equally and to prevent any movement after the injection. Most of the vehicle in the gel is absorbed and replaced by fibrin used as an intermediate spacer and during the following 3 to 4 weeks fibroblasts form collagen and it organizes itself around the silicon. So, the subject's collagen replaces the vehicle in the gel and tends to develop over time. It is always essential to take care not to overcorrect the defect but to use this filler in several sessions. The minimal interval between two injections is six weeks.[11]

Indications for use included large volumes defects on the face but also skull defects, lipoatrophy areas, and lipoatrophy defects due to liposuction and pectus excavatum. Patients with thin skin present a higher risk of complications such as overcorrection, bleaching at the injection site, and seeing or palpating the implant. This filler is contraindicated in patients with from kidney disease, presenting hypertrophic scarring history, haemorrhagic disorders, autoimmune, or inflammatory diseases.[11,12]

Complications include overcorrection, infection and foreign-body granuloma that it is possible to remove using sharp cannulas or biopsy needles.[17] The permanent nature of this product is due to its non-degradable silicone particles and to fibrous tissue response to its silicone particles that results in long-term effects. Liquid injectable silicone (polydimethylsiloxane) (LIS) is a permanent filler used for a great number of cutaneous and subcutaneous atrophies. The intervals between the sessions are generally 2 months in the first phases of the treatment. The increase takes place gradually over several treatment sessions, distributed over 3 to 9 months.[11]

The injection technique is usually the microdroplets multipuncture of Orentreich (MDT). The MDT's technique was developed by Norman Orentreich in 1952 and improved in

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1955. This technique allows the needle to be inserted subdermally in the skin with intervals of 2 to 5 mm and a release of a volume microdroplet from 0.005 to 0.01 mL. The MDT minimizes the risk to produce regrouping or pearls of silicone in the injection pathway. With LIS, the defect is deliberately under-corrected, with gradual augmentation during subsequent sessions.[11,12]

Adverse effects and complications include: pain, oedema, bruises, erythema, pigmentation or dyschromia, overcorrection, migration of the injected material to distant locations (drift), induration, and connective disease (Scleroderma) after silicone breast implants. Idiosyncratic reactions to LIS is characterized by moderate swelling with or without erythema that can appear months or years after the injection and that are frequently preceded by an infection in a distant site, such as acute sinusitis, furuncle, otitis media, or dental abscess.[12] Although considered biologically inert LIS has been reported as inducing a granulomatous inflammatory response of variable severity after tissue injection.[18] The reactions may develop many years after injection. More severe complications such as granulomatous reaction, presenting clinically as recurrent cellulites with nodule formation, ulceration, and local lymph node enlargement, have also been reported, as well as tissue scarring, embolism, acute pneumonitis, and granulomatous hepatitis.[19,20,21]

Polyacrylamide Gel

Polyacrylamide gel (PAG) is a biocompatible and non-resorbable hydrogel. It is a jelly-like transparent substance consisting of 95% water and 5% hydrophilic, biocompatible, cross-linked polyacrylamide polymer, which contains no particles.[22] It is homogenous, perfectly stable and non-biodegradable, and has optimal viscosity and elasticity. The high water contents allow a continuous water exchange between the hydrogel and the surrounding tissue and prevents biofilm formation.[11,12]

PAG must be injected strictly subcutaneously.[23] Correction is not needed at the first injection: more sessions may be performed at a 15-day interval.

Adverse reactions of infectious nature may occur within the first year after injection.[23] Gel migration has not been reported, but PAG has been found within some site-related macrophages and giant cells. Inflammatory nodules showed an increased foreign-body reaction and bacterial infection. According to the literature, those nodules occur no later than after 1 year.[11,23]

Alkylamides

It is a non-resorbable polymeric material composed of alkylamide groups. Its use is not recommended for cosmetic wrinkles but it was indicated for severe reconstructions, such as filling a facial soft tissue deficit such as facial lipodystrophy.[11,12]

Very serious defects such as pectus excavatum, Poland syndrome, postoperative trauma, in addition to common aesthetic results such as lip, cheekbone, chin hypovolumetry and relaxing of nasolabial sulcus, have been treated. Initially, aesthetics results were excellent. No migration or dislocation of the implants, granuloma, allergic response, or intolerance of any kind were observed.[11]

Karim et al.[24] reported a study from the Netherlands with 18 cases of side effects. The onset of complications can be between one month to three years, presenting as excessive capsule formation, dislocation, or migration of this implant and infection. Systemic or intra-lesional steroids and antibiotics may temporarily relieve the symptoms but the foreign material must be surgically removed to treat the infection properly.

Conclusion

Synthetic injectable facial fillers with a permanent effect are widely atoxic and nonimmunogenic, but they differ with respect to composition and in chemical and biologic characteristics. However, the fear is that the use of permanent fillers may lead to permanent problems. They all act as foreign bodies in the tissues eliciting a host response that try to remove the gel. Inflammatory nodules may develop at the sites of injection-for some fillers, many years later. So, both patients and physicians alike have eagerly sought a product to minimize the inconvenience and cost of repeated injections. Temporary injectable fillers have become so widely accepted within the cosmetic medical industry that permanent fillers with longer lasting effects are fast gaining popularity.

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