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The role of fillers in aesthetic medicine: medico-legal aspects

E. MARINELLI[1], G. MONTANARI VERGALLO[1], G. REALE[2] A. DI LUCA[3], I. CATARINOZZI[1], S. NAPOLETANO[1], S. ZAAMI[1]

[1]Department of Anatomical, Histological, Forensic and Orthopaedic Sciences, Sapienza University of Rome, Rome, Italy
[2]Department of Maxillo-Facial Surgery, Sapienza University of Rome, Rome, Italy
[3]Institute of Public Health, Section of Legal Medicine, Catholic University, School of Medicine, Rome, Italy

Abstract. – In recent years there has been an exponential increase of fillers use in aesthetic medicine. The popularity of this anti-wrinkle product is based on their capacity to offer significant improvement in the aesthetic field, particularly to skin rejuvenating processes with non-invasive and less expensive techniques, if compared to the surgical methods (i.e. surgical lifting). The great number of fillers on the market is composed of a large heterogenic number of biomaterials. The aim of this review was to provide an overview and a classification of the filling materials that are most commonly used. A synthesis of the literature concerning fillers and related side effects was also reported. The law decree no. 23 of 1998, converted in the law no. 94 of 1998 and the principal judgments of the Italian Court of Cassation have been examined with the medico-legal issues related to fillers use in medicine. With respect to their degradation, filler materials may be classified as temporary (degradable), semi-permanent and permanent (not degradable). The temporary fillers such as hyaluronic acid and collagen are completely degraded by the surrounding tissue in a few months. The permanent fillers, such as the ones derived from silicon oil and minerals are not biodegradable and may cause serious and irreversible side effects. Their use requires a physician with a high level of specialization to perform the treatment, a deep knowledge of face anatomy and a great degree of experience.

Key Words:
Aesthetic medicine, Filler, Off label drugs, Medical responsibility, Consent.

Introduction

Fillers used in aesthetic medicine are implantable medical devices, disciplined by the legislative decree no. 37 of 2010, issued after the European Community directive 2007/47/CE**,** which provided mandatory rules for all member States for their production, certification and marketing authorization. Different fillers have similar therapeutic aims, but can largely differ with respect to biological and physico-chemical features. Although being injected under the skin, fillers are not classified as medicaments, so that they have never been required to pass the mandatory tests of the pharmacopeia, apart from those used for the medical and surgical devices. Due to their composition, fillers are ideal for reduce the signs of aging, attenuate wrinkles and skin depressions remodelling the sides of the visage, restoring shape and volume to the lips, correcting imperfections due to acne or scars and augmenting the volume of the cheekbones.

The use of fillers dates back to the sixties. The first one was silicon oil, which has then been prohibited in the U.S. by the Food and Drug Administration[1] since 1991 and in Italy[2] since 1993 due to the evidence of severe side effects such as allergies, inflammatory reactions, and granulomatous reactions. Silicon is an extremely mobile and unstable substance that presents the risk to migrate towards other districts from the original implant. Moreover, being an exogenous substance for the body, there is the risk of a rejection reaction.

Subsequently, injectable products were proposed, that were based on animal derived collagen, generally from controlled bovine breeds. Collagen is part of the skin support and it can be injected to increase lips volume or to correct wrinkles, post-acne and traumatic scars. For this product, Italy and France still required a preventive cutaneous test, in consideration of the probable allergenic effects.

Generally speaking, during the last years there has been an increase in the complications related to dermic filler injections, mostly in patients that undergo multiple treatments with different prod-

Corresponding Author: Alessandro di Luca, MD; e-mail: aless.diluca@gmail.com

ucts. The imaging and histological studies may suggest the kind of substances that had been used, although it remains difficult to identify precisely the used bio-material[3].

Although there is a multitude of different products in commerce, all the fillers may be divided into two wide categories: (1) fillers that are biodegradable or absorbable; (2) fillers that are permanent or not biodegradable[4].

Absorbable Fillers

All the fillers that are biodegradable contain polysaccharides, components of the derma that tend to a progressive reduction with the aging process. When exogenously injected, they increase the cutaneous hydration filling the gaps between wrinkles. Our body can absorb these molecules in a variable time after filler injection under the skin, enzymatically digesting them or desegregating with the mimic facial movements. The time for the elimination directly influences the duration of the treatment. This duration varies between individuals, and it is influenced by the life-style (smoke habit, alcoholic or super-alcoholic abuse, excessive exposition to sunlight or sunlamps)[5].

The most common absorbable fillers are based on hyaluronic acid. This substance is a natural polysaccharide, whose absolute biocompatibility is due to the complete absence of immunogenicity and antigenicity. In aesthetic medicine, it is used to correct the volume and borders of the lips, eye wrinkles, to remodel the shape of the visage, to correct scars due to acne or trauma and imperfections of the soft tissues. The total injected volume is maintained until all the hyaluronic acid is completely absorbed by the body[6]. The effects last for 6-18 months, depending on the complexity of the used molecule and the product guarantee a good control of the possible side effects. The hyaluronic acid fillers have their natural antidote. It is called hyaluronidase, an enzyme that timely absorbs only the injected hyaluronic acid, restoring the pre-treatment situation in brief time interval and not affecting hyaluronic acid previously present inside the body[7].

Fillers based on polylactic acid are gaining more relevance. This biodegradable thermoplastic aliphatic polyester is a biodegradable, biocompatible, non-immunogenic, laboratory-crafted molecule, able to stimulate the endogen synthesis of the collagen, granting a more lasting filling effect of at least 10 months[8]. It is especially applied on the wide gaps of the nose wrinkles, to redefine the volume of the facial borders, cheeks, hands, neck and wide wrinkles[9].

Finally, glycolic acid, the smallest α-hydroxy acid, is a product with exfoliating proprieties stimulating the production of new cells that give new life to the skin, eliminating wrinkles and scars[10]. When using non-permanent fillers, the treated area may show small signs due to injection such as erythema, ecchymosis, edema and redness; all of them reversible in few days[11]. Inflammatory reactions can also occur and cause for example, edema and redness that are possibly associated with tingling, itching or pain in the injection area. This is more common in the highly vascularized areas and patients under treatment with anticoagulants or blood fluidizing integrators as omega 3, ginko biloba, ginseng, and vitamin E. No allergenic reaction has been reported and very rarely infective reactions, which are in any case due to poor hygiene in the moment of the injection.

Conversely, the most clinically relevant complications are related to erroneous or inappropriate injection techniques. Biodegradable fillers are contraindicated during pregnancy and breastfeeding, systematic autoimmune diseases or important dermatological problems and diabetes mellitus[12].

A peculiar kind of absorbable filler is represented by the lipofilling, a natural and non-allergenic method to fill a specific part of the body using fat cells drawn by other districts (usually belly, knees or thighs), that are later introduced in the areas that need to be filled. The method (Coleman's technique) consists in drawing the fat cells with a syringe and a small tubule from an area where they are abundant and to inject them with microtubules, where the filling is needed.

While the hyaluronic acid based fillers are completely absorbable, lipofilling can be considered as nearly permanent. Only a certain percentage of the fat tissue is reabsorbed (30%-40%) while more than a half remains *in situ*. This particular procedure is generally safe determining minimum percentage of foreign body reactions on the permanent fillers. Anyhow, in rare cases lipofilling can originate fat-tissue granulomas, in particular around the eyes or on the cheeks[13].

Lipofilling is probably the treatment of choice nowadays, being fat a self-product. Main disadvantages are the need of a "donor site" that increases related complications and procedure timing as well as greater post-operative care.

Permanent or Semi Permanent Fillers

Permanent fillers, composed by microspheres of plastic material that is not absorbed and remain

in the body, are considered part of the off-label prescriptions, meaning that they are used for a different therapeutic purpose on the one they were experimented for and therefore commercialized. Such different use, anyhow, is admitted only when there are the circumstances described in the article 3 of the law decree of 17 February 1998, no. 23 which states that: a) the physician determines, on the base of documented facts, that the patient might not be successfully treated with conventional medicaments that are already approved for the specific therapeutic indication (or that peculiar way or mode of administration); b) the use is known and compliant to studies published in scientific journals with international acknowledgement; c) the patient has to sign a written consent before treatment[14]. E.g. there are fillers, which have been approved for the correction of moderate to serious wrinkles, but the physician can decide under his responsibility to use them also to treat little imperfections of the nasal profile. On this matter, the deontological code is decisively more flexible. Indeed, article 13 allows the off label use if the tolerance and the efficacy of the treatment are scientifically found and the risks are proportionate to the expected benefits. Anyhow, article 13 also requires the written consent from the patient and establishes that the physician has to evaluate the effect of the treatment over the time. Therefore, it is imperative that the physician is more cautious in controlling the development of the treatment.

Permanent fillers behave as foreign bodies, which determine a reaction of our body defined as a chronic granulomatous reaction. They are injected in the deep derma and give the advantage of providing a long-term correction that does not force the patient to periodically refilling. The effect lasts for about two years. After this time interval, there is a need for a new treatment. The use of permanent fillers is very rare in Italy.

There are several reasons to avoid their use: first, being permanent and not biocompatible, they can be the cause of irreversible side effects. Moreover, once injected, the permanent filler may only be eliminated by a surgical removal of the tissue where the injection had taken place since it penetrates into the connective tissues.

If the foreign body reaches a silent plateau state, the reaction can neither be seen nor felt with the touch. Sometimes, however, the reaction becomes acute and large, hard and aching nodules are formed under the skin modifying the patient appearance so that surgical or cortisone-based therapies have to be performed to remove the nodules, even if these two interventsions can not always solve these problems. This kind of filler obviously has its own weight and density that, during the years, cause a slow migration of the substance itself from the injection site due to the force of gravity[15]. The effect is a progressive visibility of the filler in a different area, determining a "swollen effect" (as an example "fish lips"). In the case of fillers that are injected in areas that are not on the facial surface, as limbs or bottom, a very visible and anti-aesthetic formation of nodules or migration of the substance for various centimetres or tens of centimetres from the injection area can occur. There are known cases of cheekbones migrated towards the jawline, hips towards the thighs (in some cases down to the ankles). In other cases, the physiological modification of the visage or peculiar alterations of the body weight, as important weight losses, can render the foreign bodies and injected material visible with clear anti-aesthetic results[16].

Medico-legal Issues

Risk management has become a protagonist in the health care scene, especially in a field such as that of aesthetic medicine, where the customer satisfaction has a relevant role. Although the treatments are considered as "light", the ambulatory follow-up is mandatory to grant hygiene-sanitary standards that minimize the infective risks. To achieve such goal, it is necessary to accurately sterilize the site of the filler injection with a non-alcoholic disinfectant, to remove cautiously the needle and the syringe from its single sterile confection, to wear gloves during the procedure and to avoid injections in patients with a history of herpes infections.

It is important to act in places with fully equipped facilities to better face any possible complication, besides the infective ones. Applying fillers is, in fact, a fairly simple procedure; yet if not well performed or with substances that are enough "safe" it might cause unwanted side effects and sometimes damages, that are legally framed as an unjust damage to the patient and therefore compensable[17]. Thus it is significant for physician having an adequate training: it was demonstrated that a methodization of teaching facial dermal filling is effective in reducing adverse effects caused by indication errors, product choice or technical execution." e inserire un'altra voce bibliografica che diventerebbe la numero[18].

During the first medical examination, the physician should proceed in collecting a detailed anamnesis from the patient and to a cutaneous check-up with particular attention to the feature that needs correction. This should allow him to choose the product that is more appropriate for the specific condition of the single patient[19]. From a medico-legal perspective, the evaluation criteria of the aesthetic results are based essentially on the comparison between the previous state and its modifications; therefore, it is preferable to collect photographic documentation to allow the physician accurately evaluate the visage features of the patient and determine which kind of fillers are more indicated and where they have to be applied and in which amount.

Moreover, by these means, the physician may have available objective data that do not allow any speculation in case of litigation. The documentation should contain the patient personal information, anamnesis, written consent, the description of the procedure and of the material that has been injected. The indications and prescriptions adopted to prepare the skin for the injection of the filler should also be reported. It is also necessary to perform an intradermic test to evaluate the cutaneous reactivity. A negative test does not exclude utterly possible complications, while a positive test represents an absolute contraindication to the treatment. The physician has to declare to the patient all the contraindications to the filler injection, as advanced pregnancy, infective recurrent dermatosis as herpes, constitutional scar tissue hyperactivity, and autoimmune diseases and skin hypersensitivity. Patients with dental infections have increased risk for granuloma; hence, a dentist check-up is recommended. A further problem regards the origin and the safety of the used products. Indeed, in some cases some fillers have been found contaminated with *pseudomonas aeruginosa,* a bacterium responsible for serious infections.

The health professional has to provide the patient with a detailed indication of the treatment and inform him about the possible side effects and the estimated time window of the treatment, asking him to sign forms for the written consent that need to be clear and detailed. Furthermore, it is advised to provide the patient with some informative brochures about the techniques and used materials[20].

Once the treatment has been executed, the physician has to inform the patient about the precautionary measures he/she has to follow in the days after the treatment. Forgetting to provide these simple "precautions" may expose the doctor to the responsibility for omitting important acts, as well as breaking article 33 of the Italian deontological code[21].

In clinical practice, follow-up is essential to prevent complications and to make patients responsible, since many of them do not pay particular attention to medical guidelines.

According to some rules, even if the patient chooses to undergo to a certain filler treatment, he/she has to ask about the features of the proposed filler, make sure that the filler origin is traceable and hence provided with a label. He/she has to ask for the identification name, lot number, expiring date of the product and to know how it will react in different time lapses.

Many doctors have recently introduced the so-called "Body Passport". It is a medical record provided to the patient that reports any treatment performed and product used. Unfortunately, some patients do not care about the origin and the nature of the filler, choosing and buying it online with a "coupon" at a favorable price. This practice should be condemned: patients tend to underestimate medical procedure and post-treatment care and in this way doctors vulgarize their profession, considering patients as "customers".

Those patients should also ask for information regarding the possible side effects and if they had already been treated with a different substance, they have to provide to the physician the information about the used substance since the association between substances of different origin might prove harmful[22]. A detailed anamnesis is mandatory: many patients are well aware that previous treatments could make impossible or hazardous a new procedure and then they often "forget" to inform doctors.

The Consent to Aesthetic Surgery for Dermal Fillers

To avoid judiciary and deontological consequences, the medical-surgical activity has to be always preceded by the signed consent of the patient, since the latter has the right to choose between the different possibilities offered by the physician, that he may also completely reject or knowingly interrupt. The consent should list the possible side effects of the therapy with the eventual contraindications, and the potential severity of the treatment effect.

Regarding aesthetic surgery, the Courts usually affirm that the information provided to the patient, in this case, has to be more detailed when compared to other surgical matters[23]. The reason

resides in the fact that the person requesting the treatment is healthy and decides to undergo a voluptuary procedure, without any urgency and hence he/she should be informed at the best[24,25].

In our opinion, the informative duty in the aesthetic field should be identical to the one expressed in other fields of surgery and the information should not need to be more extensive, but only more accurate concerning two aspects[26].

First of all, it is necessary to let the patient understand how many chances of a positive result exist and which aesthetic modification is realistically achievable. Indeed, sometimes, the patients do not perceive the treatment just as a measure to eliminate some physical imperfection, but also as a mean to resemble as much as possible an established model (e.g. a famous character). Consequently, although the result might be considered satisfactory, it might not satisfy the patient expetations[27].

Another delicate matter is the timing of all the procedures. The treatment is not required for health problems, but just for aesthetic ones, and this creates a major time lap necessary between the first medical examination, the information procedure and the subsequent consent to the treatment. This is necessary for the patient to deeply analyze the opportunity to expose his/her health to a potential risk for exclusively aesthetic matters.

The consent represents an authentic document with legal value, whose aim is to safeguard both the physician and the patient from mistakes o incomprehension. The physician has the duty, during the pre-treatment examinations, to provide the patient with a number of details that are indispensable for an evaluation of the different procedures with the aim to arrive at a final and correct choice: the consent provides only a list of the received information and certifies that it has been fully comprehended. Also, the consent is used to collect authorizations, mostly regarding the possibility of emergency treatments or specific use of the clinical and photographic documentation.

By the correct standards of the best medical practice, the physician has the duty to provide the patient with the following information:

1) Available techniques aimed to solve the patient problem, with the indication of the advantages and disadvantages of each (in case of therapeutic and not aesthetic procedures, the information should include the possibility of not undergoing the procedure with the possible consequences of this decision);
2) Description of the general risks of surgical interventions and detailed explanation of the complication specifically connected to the procedure desired by the patient. The list of the latter has to be clearly present in the consent together with the frequency of each complication and the indication of the therapies that are possible in case of such events, and preferably, clearing how the expenses of the procedure are charged;
3) Description of the use or not of anesthetics during the procedures and explanation of the possible risks connected to them;
4) Description of the therapies and clinical controls necessary to be performed after the treatment, together with the risks connected with the lack of the post-surgery controls;
5) How to fill and use clinical and photographic documentation[28].

The highest level of the Italian justice has also confirmed the importance of the above-reported information. In two different judgments, the Penal Cassation Court[29,30] condemned two physicians, responsible for a superficial anatomical alteration that caused permanent effects to the patient's health, for unintentional injuries. The used filler contained substances, which caused the formation of foreign body granulomas of the skin and this complication, although more frequent when using non-medical-grade silicone[31], might appear after months or years after the treatment[32,33].

In the second case, the injected substance was Bioalcamid, a polyalkylimide that, as in the case of other permanent fillers, presents the risk of such serious complications, that may cause real deformities (even after years) as a consequence of the migration of the material[34]. The physician fault consisted in not providing enough information about the possibility of those specific complications due to the injection of the substance. It was a predictable consequence that should have been specifically explained. Moreover, especially because it was an off-label substance and hence not adequately experimented, the exhaustive information to the patient was even more important. We have not to forget that the patient pursues a result that is not declinable regarding health protection, it is presumable that if adequately informed about the risks of the treatments he/she would not have provided consent. Thus, the Supreme Court ruled that, especially in cases where surgery is not necessary for the protection of patient life or health, the consent may not only simply contain the communication of the product name that will

be administered or a generic information. Conversely, any adverse effects related to the injection that would allow the patient to suitably assess the cost-effectiveness of the treatment should be communicated and the existence and severity of conceivable consequences taken into account.

On the one hand, these judgments highlight the need to develop guidelines that regulate the medical and legal aspects, such as medical records and informed consent[35], on the other, they should alert physicians to a respectful attitude and strict diligence, skill and prudence because "the best way to deal with medicolegal problems is to avoid them. It is better to be safe than sorry"[36]. In this concern, a common EU law is mandatory for the harmonization of patient rights and medical procedures in different countries from Europe.

Conclusions

One of the most required results in aesthetic medicine is the creation of a product that will give permanent, stabile and safe results. Since at the moment such kind of product is missing, patients face the alternative between choosing absorbable products that force to new treatments every four-six months, or permanent, whose effects are enduring but may cause serious damages.

The authors believe that the use of absorbable fillers is always preferable since they do not cause theoretically any side effect. A substantial knowledge of the chemical features of the substances has to be provided by the physician. In this way, the patient is informed of the potential side effects of the treatment and can avoid serious complications while obtaining optimal results. Most of all, the patient should have the possibility to choose if continuing the treatment or returning to the natural condition.

Authors Contributions

All the authors made substantial contributions to conception and design of the manuscript; E.M. and S.Z wrote the paper, I.C and S.N. performed the literature research, G.MV and G.R. revised the manuscript. All the authors have been involved in revising the manuscript critically for important content and all of them have given final approval to the version to be published.

Conflicts of interest

The authors declare no conflicts of interest.

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