Injections of soft tissue fillers belong to the most commonly performed beautifying measures worldwide. The number of commercially available fillers is increasing rapidly, resulting in a myriad of injection options. Novel fillers are continuously launched on the market, whereas old ones are chemically modified to increase their tolerability, ease of injection, or duration and to reduce potential side effects. The filler market is tightly regulated within the European Union and North America, but obviously not in many other countries. Apparently, low-priced products of poor quality continue to create irresistible temptation for both patients to reduce expenses and injectors to increase financial profit. Injections should exclusively be performed by trained and experienced medical doctors. However, we suspect a large number of injections being performed by nonprofessionals at low costs. The combination of unapproved products of poor and questionable quality with nonmedical injectors is particularly dangerous and can have fatal consequences. For instance, illegal cocktails of oily vitamin-containing substances applied by cosmeticians result in poor clinical outcome and regularly lead to devastating complications. But even cautious handling of fillers by professionals may result in serious adverse effects or trigger other health disorders such as herpes simplex outbreaks in a person with the history of frequent herpes simplex episodes.

It is the treating physician’s obligation to inform the patient about the nature and frequency of filler-related side effects and to temper high expectations and unrealistic demands. Further, it cannot be overemphasized that clients with unrealistic expectations and body dysmorphic disorders should not be treated, as they will not be satisfied and tend to sue the treating physician. Most of these do’s and don’ts are well known and redundantly repeated in the literature. However, this fundamental warning is often not respected.

This edition of Facial Plastic Surgery gives an overview of adverse filler effects and is intended to give advice on how to diagnose, avoid, and treat.
Adverse Effects of Fillers and Their Histopathology

Eckart Haneke, MD, PhD

1 Department of Dermatology, Inselspital, Universitätsspital Bern, Bern, Switzerland

Address for correspondence: Eckart Haneke, MD, PhD, Department of Dermatology, Inselspital, Universitätsspital Bern, Freiburgstrasse 14, 3010 Bern, Switzerland (e-mail: haneke@gmx.net).

Filler injections belong to the most frequently performed beautifying procedures in cosmetic medicine. Untoward adverse effects are a catastrophe for the affected person and everything possible must be done to avoid them. This starts with a careful and thorough patient history concerning previous injections, potential symptoms of body dysmorphic syndrome, allergies, immune reactions and diseases, drug treatments, particularly those with an immunomodulatory potential, and chronic infections as well as a family history as to serious diseases, so-called collagenoses, immune defects, genetic disorders, and others. It is well known that some fillers are not well tolerated when injected next to another one.

Filler adverse effects can be classified according to their time course and because of user dependent, filler and host factors. Technical errors concern too much or too little volume, incorrect depth of filler placement, wrong location, and inappropriate product choice.

The physician injecting the filler must, of course, be experienced to avoid gross mistakes concerning the site of injection, the volume, the speed, the depth, etc., as well as the postinjection treatment. The physician should be available after the injection and never dismiss a patient’s concerns. The nature of complication is checked and can be classified into light and disappearing by itself, moderate and requiring treatment, or severe necessitating immediate intervention. Treating a patient with empathy has avoided many law suits.

Concerning the fillers themselves, it is the substance and its chemistry, its purity, homogeneity, particle size, shape and roughness, its electrical charge, its ability to biointegration and to react with other substances that matter. It has also to be kept in mind that a filler result that is desirable at the age of 20 years might look odd at age 50 or 60 years. And finally, the host and his or her immune system are of paramount importance. This can change during the life of a filler and have a great impact on its tolerability.

Time Course of Filler Effects

Fillers are divided into reversible (early or temporary: collagens and hyaluronic acid [HA]; late or long-term: HA with dextranomer beads, poly-L-lactic acid [PLL] and calcium hydroxylapatite), and irreversible (delayed or permanent ones: paraffin, silicon preparations, polymethyl methacrylate microspheres, hydroxyethyl methacrylate fragments, polyacrylamide hydrogel, polyalkylimide gel, polyvinyl hydroxide microspheres in polyacrylamide gel, and many more). In general, their adverse effects last as long as their intended ones.

Although it is often thought that temporary fillers are better tolerated than permanent ones, this is apparently not true as the frequency of short-term adverse reactions is very similar. In fact, whatever substance is injected into the tissue, it is perceived as a foreign substance with an initial challenge to the host’s immune system. The famous injections of the patients’ own blood had an nonspecific immunostimulatory effect as even this was a short-term challenge to the immune system. The famous injections of the patients’ own blood had a nonspecific immunostimulatory effect as even this was a short-term challenge to the immune system.

Early complications develop within less than 2 weeks and include erythema, edema, and allergy. Bumps and lumps following superficial injection are usually visible immediately

Abstract

Keywords

► adverse effect
► filler
► histopathology
► complication management

Injectable fillers nowadays represent a pillar in facial rejuvenation and make a significant contribution to the success of the treatment. Despite their obvious benefits, a wide range of possible complications such as immediate, late, delayed, temporary, or irreversible adverse effects have to be respected. Differentiating the various filler materials, these effects are assigned to histopathology findings and currently available treatment options.
after the injection or shortly thereafter. Necrosis because of intra-arterial injection becomes obvious within a day.

Late complications are chronic inflammation, late allergic reactions, nodules (granulomas) and filler migration, hypertrophic scars, and telangiectasia.5

Delayed complications are considered to be largely because of biofilm formation although this is still disputed.7

Often, adverse effects develop weeks, months, or even years after the injection, and the patients frequently do not remember which filler they had gotten. The problem may even be confounded by the fact that different fillers may have been injected at various times by different physicians and even sometimes by nonphysicians.

Immediate reactions such as adequate pain after procedure, mild bruising, redness, and some edema are normal and are not complications. They can often be avoided by cooling the injected area, and this is also the most common treatment. Pain can be reduced by local anesthesia, slow injection, and low volume. Aloe vera, arnica, or vitamin K creams are recommended to reduce or avoid bruising. Bleeding and ecchymoses are rare when blunt cannulas are used. Swelling depends on the substance used, the localization of the injection, the amount, and the individual tolerance. Again, cooling usually reduces the swelling.

Vascular compromise may be the consequence of arterial or venous obstruction, which in turn may be because of intravascular injection of the filler, direct pressure of the filler on the vessel wall, or indirect trauma to the vessel wall. Particular attention has to be paid during glabella and nasal ala injections where inadvertent intravascular filler injection may result in necrosis and even blindness when the retinal artery is occluded.8,9 Whenever blanching is seen during the injection this must immediately be stopped.10 In case of HA, hyaluronidase is injected as close to the site of intravascular injection as possible. Whether aggressive massage, warm compresses, and nitroglycerin application are really helpful for other fillers remains to be seen.11–13 Intravascular injection is virtually impossible when using a blunt cannula.14

Late complications are infection, granuloma formation, scarring, and loss of function. Infection may be because of insufficient disinfection of the treatment area, injection into or through an oily skin or makeup or into an infected region.15 Infection can develop into a major problem when particulate permanent fillers are used that may develop a bacterial biofilm on the surface of the particles. Although cellulitis promptly responds to systemic antibiotics biofilms are usually resistant to antibiotics and require complete removal of the filler.16 Granulomas are another serious problem. There are some general rules as to their development: nonparticulate substances rarely produce granulomas with the exception of silicon, but all the particles may induce granulomas. The frequency of granulomas is the higher the bigger the surface is in relation to the volume, the sharper the edges of the particles are, that is, crystalloid particles are much more likely to induce granulomas independent of the longevity of the particles. PLL acid is a slowly dissolving crystalloid compound that caused several granulomas, particularly, at the time when the recommendation to reconstitute it with a small volume of saline was followed by the users.17 Although some permanent fillers are advertised as being gels they may consist of small polygonal particles, such as polyacrylamide gel (PAAG) or hydroxyethyl methacrylate (DermaLive and DermaDeep; Dermatech, Paris, France).

Delayed reactions are thought to be because of bacterial biofilms.18 They may induce granulomas as well as so-called cold abscesses. This is the reason why granulomas should not be injected with corticosteroids as the first therapy but rather be treated with antibiotics for at least 14 days.

Classes of Soft Tissue Fillers

General Remarks
Many different agents are available. Some have the same or very similar names and are chemically different whereas some popular substances are sold under many different brand names.

The same agents may display different behavior, due to variations in the production process, different molecular size, and variable protein moieties. This is particularly the case of the innumerable HA products.

The clinical appearance of adverse effects of the various products does not usually allow for identifying the filler used, as they are in most cases not filler specific.

Soft tissue fillers are subdivided into the following:

- Human substances
- Biologic agents
- Synthetic products

Be aware that “biological” does not automatically mean degradable and that “biodegradable” is not a guarantee that the human body has the necessary enzymes to digest this filler.

Autologous Fat

Autologous fat is the prototype of a human substance and is often thought of as being without adverse effects. However, fat injections also have potential adverse effects. They are because of collecting the fat, fat storage or injection and reach from rapid disappearance to infection and even death due to inappropriate injection technique.19

Collagen

A great number of biologic substances are on collagen basis: human collagen, bovine collagen, and porcine collagen with bovine collagen having been the first commercially available product, for example, Zyderm (McGhan Medical Corp., Fremont, CA). The degree of cross-linking and the chemical used for it also influence the tolerability of collagen fillers.20

It was thought that human collagen would have an advantage as it does not require preinjection tests as bovine collagen. However, it turned out that apart from the allergic reactions, the human collagen has virtually the same life span and may be associated with as strong inflammatory reactions as bovine collagen.21 In contrast, morselled autologous dermis appeared to be very well tolerated with only transient inflammatory reaction during the wound-healing phase and
effective revascularization.\textsuperscript{22} Collagen is also synthesized by cultured fibroblasts (Cosmoderm [Advanced Tissue Sciences, San Diego, CA] with 35 mg/mL, Cosmoplast with 65 mg/mL, and Cosmoplast with 35 mg of glutaraldehyde-stabilized human collagen/mL). Human collagen from cadaveric dermis (Dermalogen [Collagenesis, Inc., Beverly, MA] and Cymetra [Life Cell Corp, Branchburg, NJ]) is available, too. Human collagen is also produced by injected fibroblasts (Isolagen [Fibrocell Science Inc., Exton, PA]). They are cultured and expanded from a small biopsy of the patient and reinjected. Although said to give good results the procedure of taking a biopsy, sending it to a specialized laboratory, waiting 6 to 8 weeks until getting the expanded cells and the high cost have prevented it from becoming a popular method.

Porcine collagen was found to last longer and be better tolerated than bovine collagen and not require pretesting.\textsuperscript{23,24} However, lip injection is discouraged.\textsuperscript{25}

**Hyaluronic Acid**

HA is a linear, unbranched, high-molecular-weight glycosaminoglycan, consisting of alternating \(\beta\)-glucuronic acid and \(N\)-acetyl-\(\beta\)-glucosamine. As a biologic substance without species specificity, it should, in principle, be tolerated by all the living organisms. However, the natural glycosaminoglycan moiety is linked to species-specific proteins and also the production process is critical. HA is not only a biologic and naturally occurring filler, but it also has a variety of different biological effects that depend on its molecular size.\textsuperscript{26} Small fragments are proinflammatory whereas long chains inhibit inflammation.\textsuperscript{27–29} For its use as a filler, it has to be stabilized and the way and degree of stabilization are also important for the tolerability of HA.\textsuperscript{30} The more HA is cross-linked and thus stable the more its tolerability is reduced.

**Perhydrosqualene and Collagen-Polyvinylpyrrolidone**

This has recently been proposed as a filler for deep nasolabial folds with a lifetime of 12 to 18 months. It was claimed that no significant adverse effects were seen.\textsuperscript{31,32}

**Polycaprolactone**

Polycaprolactone-1 (PCL-1) dermal filler (Ellanse, AQTIS Medical, Utrecht, the Netherlands) is a soft tissue dermal filler based on PCL microspheres. The totally smooth spherical-shaped PCL microspheres (range, 25–50 \(\mu\)m) are homogenously suspended in a tailormade aqueous carbonyl methylcellulose (CMC) gel carrier. PCL in CMC has been widely used in many medical devices. It is totally biodegradable, nontoxic, and completely excreted from the human organism. The CMC gel carrier is gradually resorbed by macrophages over a period of several weeks, during which the PCL microspheres trigger a natural response of the skin and stimulate a natural wound-healing process with neocollagenesis. The new collagen replaces the volume of the resorbed carrier. The microspheres are not phagocytosed because of their size and surface characteristics. The PCL dermal filler is indicated for deep dermal and subdermal implantation including hand rejuvenation. Adverse effects were not (yet) reported.\textsuperscript{33,34}

**Biologic, but Not Enzymatically Degradable by Humans**

Alginate-derived mannans were thought to offer advantages over other short-lived biological fillers because of their ease of injection and lower tendency to cause swelling as compared with HA, but they soon turned out to have a high rate of adverse effects, particularly granuloma formation.\textsuperscript{35} Less than half a year after its launching the product was withdrawn from the market.

**Long-Lasting Fillers**

The currently used fillers with a long-lasting effect are PLL and calcium hydroxyl apatite (CHA). The former has been used for more than half a century as suture and other material in surgery and proven to be well tolerated. CHA has been used as bone cement with good effect. However, both substances are different in particle size and shape when injected as fillers for soft tissue augmentation. Granulomas were observed after PLL injections and rarely after CHA.

**Permanent (Irreversible) Fillers**

There is a huge number of different substances that had been or are still in use for soft tissue augmentation. The main classes comprise polymethyl methacrylate (Arteplast [Suneva Medical, San Diego, CA], Artect [Artes Medical Inc., San Diego, CA], Artefill [Suneva Medical], Metacril [Nutricell, Rio de Janeiro, Brazil], and Metrex [Nutricell]), methacrylate fillers (ProCell [ProCell Therapies, Clearwater, FL]), acrylic hydrogel (DermaLive, DermaDeep), PAAG (Amazing gel [Nan-Feng Medical Science and Technology Development Co., Ltd., Shijiazhuang, China], Aquamide [Contura International, Söborg, Denmark], Argiform [Bioform Corp., Moscow, Russia], Bioformacyl [Progen, Ancona, Italy], Evolution [ProCytech SA, Bordeaux, France], Formacryl [Progen], and Outline [ProCytech SA]), polyethylene beads (Profil [Laboratoires Filorga, Paris, France]), polylalkylamide (Bio-Alcamid [B&B Dental SRL, Polymekon, Italy]), solid silicone particles in polyvinylpyrrolidone (Bioplastique [Netherlands]), polydimethylsiloxane (Biopolimero [Spain] and Biopolymere [Biocell Laboratories, Lichtenstein, Germany]), silicone oil (medical grade silicone oil), polymeric compound of natural silica and oxygen (Dermagen [Dermagen Inc., Fullerton, CA], polyoxymethylene fatty acid and elastin copolymer gel (Kopolymer 4G [Switzerland]), methacrylate and copolymer 4-G (Rhegecoll [Switzerland]). Some are illegal in the United States and the European Union, others have been withdrawn from the market for several years, but they continue to induce granulomas and other severe adverse effects. Chemically similar or even identical substances are marketed as different particle size and shape and exhibit very different adverse effect profiles.

**Adverse Effects**

Many adverse effects are not specific for a particular filler but may be ascribed to the volume augmentation or to technical faults such as wrong indication, placement site, wrong injection needle,\textsuperscript{36} and infection due to contaminated ice or water.\textsuperscript{37} Infections can best be differentiated from other nodules and granulomas by radio-labeled leukocyte scintigraphy.\textsuperscript{38} Late-onset adverse effects are often inflammatory...
and immune mediated. Edema, granulomas, sarcoid-like reactions, and panniculitis are the findings most commonly seen. Systemic granulomatous and autoimmune diseases, and even less frequently, acute hypersensitivity reactions are rarely seen.40

**Autologous Fat**

Adherence to key principles, including sterile technique and low-volume injection throughout layers of tissue, is critical in obtaining excellent results. Adverse outcomes are infrequent. However, early adoption of surgical procedures by those without a sound understanding of the underlying principles and techniques can have disastrous consequences. Furthermore, physicians operating on any patient must understand the potential for complications and be able to manage these appropriately when they occur.41 Fat longevity is dependent on handling and preparation of the fat. Poor fat viability produces an inadequate result and has thus to be considered as a complication.42 On the contrary, deterioration of the esthetic results after a significant weight gain because of corticosteroids, oral contraception, and a change of lifestyle was seen in a patient with Romberg syndrome.43 Lipomodeling of the breast was performed in 880 cases, approximately 140 mL had to be injected for a desired volume of 100 mL, which remained stable for 3 to 4 months. No radiological problems at mammography were observed after the procedure. Fat necrosis occurred in only 3%, but serious complications included one case of infection at the harvest site, six cases of infection at the injection site, and one case of intraoperative pneumothorax.44 Furthermore, there are case reports on an abscess formation, life-threatening sepsis, and residual deformity.41 Neurological complications were repeatedly reported by two patients developing unilateral loss of vision after fat injection into the glabella, two patients with loss of vision, aphasia, and hemiparesis, and one patient developing sensorimotor hemiparesis after infarction of the middle cerebral artery.45–48 Death after autologous fat grafting occurred in a 20-year-old woman with a decade of lupus profundus and hereditary C4 complement deficiency who had already got three fat injections from 1997 to 1999 with approximately 50% resorption. A flare of her lupus profundus in 2007 resulted in loss of most of the injected fat despite treatment with thalidomide 25 mg and prednisolone 7.5 mg daily. After donor site tumescent anesthesia and bilateral infraorbital blocks for recipient sites, 35 mL fat were injected with minimal pressure using an 18-gauge sharp needle because of scarring of the recipient site. There was dizziness immediately after injection of the left cheek and a vasovagal syncope suspected and the patient placed in supine position. Another 35 mL of fat was subsequently injected. The patient became increasingly unwell over the next 2 hours, eventually developed progressive refractory hypoxic respiratory failure and cardiovascular decompensation. Despite emergency treatment in a critical care unit, she developed fulminant pulmonary edema, right ventricle dilatation, and died because of cardiac arrest 4 hours after fat transfer.19 Whether or not using a blunt cannula would have prevented the death of this patient is not clear. Apparently, these adverse effects were technique dependent and not due to the substance.

Liposuction is often used to collect fat and is a very safe procedure when performed under tumescent anesthesia. Infection, bruising, hematoma, and seroma are rare. Fat embolism is very rare when not too much is aspirated and liposuction is not associated with other cosmetic procedures. Most of the serious complications were associated with general anesthesia.

**Human Collagen**

Autologous human collagen is well tolerated, both when derived from cultured fibroblasts as well as autologous...
injectable dermis. Human allogeneic collagen was observed to elicit acute to subacute inflammatory reactions but no serious long-term adverse effects were reported. The cosmetic effect lasts between 4 and 7 months.

**Nonhuman Collagens**

They are foreign proteins with a propensity to induce allergies and granulomas, particularly bovine collagen whereas human and porcine collagens are better tolerated. The adverse effects are usually temporary until all collagen has been resorbed, but one case was observed with stone-hard granulomas not disappearing with any treatment over more than a decade (A. De Coninck MD, personal oral communication, 2008). Usually, the granulomas are palisaded around amorphous eosinophilic material representing bovine collagen (Fig. 1). This is characterized by very thick bundles, pale gray–violet staining with Masson trichrome stain, and lack of birefringence. Whether the injection of collagenase would be successful has not yet been tried. The most common adverse effects were temporary granulomas at the site of injection in approximately 4% of the patients. Testing and double testing before treatment were recommended, but nevertheless, granulomas did occur.

Collagen fillers are now used less and less frequently and adverse effects are expected to be seen rarely.

**Hyaluronic Acid**

HA is universally present in all animal species. It is said to be non–species specific; however, hyaluronans are linked to proteins that are species specific. Good preparations are (almost) free from foreign proteins. They have a low propensity to induce granulomas, but they show a variety of transitory adverse effects, including rare granulomas and infection. At present, there are probably almost 200 preparations on the market. To prevent untoward adverse effects well-known brands with high quality should be preferred as their complication rate has been shown to be much lower.

Untested cheap products should never be used.

HA preparations are currently the most widely used fillers with a longevity of approximately 6 months, but this is highly variable depending on molecular size and cross-linking. There are differences among them concerning the size of the molecule, the protein content, the chemical bonding, the fluidity, whether they are monophasic or biphasic, injection pain, and longevity. A good preparation must not clump as this may give rise to granulomas (Fig. 2). Although granulomas were not rare at the beginning of the non–animal–derived synthetic HAs, they are now exceptional, except for a new product marketed roughly 3 years ago. This induces foreign body giant cell granulomas with a high content of eosinophils, and HA can be seen in giant cells (Fig. 3).

Also in the early period of HA fillers, reactions interpreted to be hypersensitivity were observed. Very rare adverse effects are a multiform rash and systemic anaphylactoid reactions after intra-articular injection of HA with native HA having a lower sensitizing potential.

Adverse effects because of the substance are usually short-lived and can be repaired by injecting hyaluronidase. The dose depends on the specific drug and may also vary according to the HA used and its degree of cross-linking. This enzyme cleaves both natural as well as cross-linked HA. Three sources available are as follows: bovine, ovine, and recombinant. As they are proteins, they have the potential of causing an anaphylactic shock in sensitized individuals. It is therefore necessary to question the patient about possible allergies. Hyaluronidase has also been used to treat HA granulomas.

Technique-dependent adverse effects may occur as with other fillers. When HA is injected too superficially, it may shine through with a bluish-grayish color, giving rise to the
so-called Tyndall effect. It has to be used with care in the eyelids as it may cause swelling due to its ability to attract water. Accidental intracapillary injection may cause livedo reticularis.

Histopathology of grayish-glassy nodules after superficial injection just show HA deposits without any further tissue changes (Fig. 3). Granulomas may show a very dense lymphocytic infiltrate with abundant eosinophils and many foreign body giant cells often containing basophilic amorphous material that corresponds to HA (Fig. 3).

A middle-aged woman was seen with widespread swelling in the glabella, central ocular, and nasal regions after she had injected herself with a diluted HA-containing cream for topical use; histopathology showed a “Swiss cheese like” picture similar to that after vaseline injection; this adverse effect was most probably not due to the HA component in the abused topical preparation (unpublished personal observation).

**Alginate**

An alginate derived filler (Novabel CellMed AG, Merz Pharmaceuticals, Frankfurt am Main, Germany) was marketed as a new biologic filler with prolonged augmentation effect; however, very shortly after its marketing, granulomas were observed and it was withdrawn from the market. The granulomas start with erythema and swelling until hard nodules form 2 to 5 months after injection. Ultrasound shows hypoechoic structures surrounded by a hyperechoic rim. Histopathology demonstrates spherical basophil structures of 100 to 120 µm in diameter enveloped by a prominent rim of giant cells. The granulomas are surrounded by a distinct hyaline capsule.

**Hyaluronic Acid Plus Dextranomer Microspheres**

The dextranomer beads are added to the HA to improve the longevity of the filler. They consist of cross-linked dextran molecules with a positive surface charge and a diameter of 80 to 120 µm. They attract macrophages releasing tumor growth factor β and interleukins, which stimulates collagenesis around the dextranomer beads, maintaining the volume correction effect after the resorption of HA. The material is apparently well tolerated with only a few reports of granulomas (Fig. 4), one of which was suppurative and the other ones were foreign body giant cell rich. In histopathology, the dextranomer beads stain dark bluish or

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**Fig. 3** (A) Inflammatory and granulomatous reaction to hyaluronic acid (Hylacorp [BioScience GmbH, Ransbach-Baumbach, Germany]). HE, ×100. (B) Foreign body giant cells engulfing clumped hyaluronic acid (Hylacorp). (C) Epithelioid cells, foreign body giant cells with ingested hyaluronic acid (Hylacorp) and a very dense eosinophilic infiltrate.

**Fig. 4** Sterile suppurative granulomas due to Matridex (Courtesy: G. Feller-Heppt, Germany).
purplish, or may even look like empty spaces giving a “Swiss cheese” aspect. Incision of the nodules and treatment with cephalaxin and methylprednisolone aceponate led to complete resolution in one case.63

**Poly-L-lactic Acid**

This substance has been used for decades in medicine and surgery and was well tolerated. In contrast, PLL as a filler comes as a powder of crystalloid particles that has to be reconstituted before injection. Subcutaneous nodules are either fibrotic or granulomas. They can form because of insufficient time during reconstitution of the material, inadequate dilution, overcorrection, superficial injection techniques, or inappropriate concentration of PLLA molecules secondary to muscle movement, and granulomas are thought to be because of allergic or inflammatory host responses.66 In the early years, the recommendation was to use 3 mL: this turned out to cause granulomas and also often clogged the injection needle. Now, most physicians use 10 mL or more of physiologic saline, often with some lidocaine added. After injection, the water is resorbed and the PLL particles induce a fibroblastic reaction lasting for 24 months or longer. This may cause fibrotic nodules, which may be visible in thin skin such as around the eyes and in the hands,67 and the substance may clump in the lips; these are the adverse effects of faulty technique (►Figs. 5 and 6). PLL granulomas are classical giant cell granulomas with many epithelioid cells and relatively few lymphocytes. The PLL particles are oval, fusiform, or spiky and seen in epithelioid and giant cells as well as in between (►Fig. 7). They are birefringent in polarized light.17 The granulomas last at least 18 months.68

**Calcium Hydroxyl Apatite**

CHA is an inorganic material and has long been used successfully as bone cement. The currently available preparation is Radiesse (Bioform Medical Inc., San Mateo, CA), which consists of microspheres (30%) of 25 to 45 µm suspended in a gel made of water, glycerol, and sodium carboxy methylcellulose (70%). It is inert and nonantigenic, but it stimulates collagen production. It is very well tolerated when injected as a suspension for soft tissue augmentation. The duration of the correction is between 9 and 12 months,69 but it may also be longer. Most adverse effects are because of technical faults. Particularly when injected into the lips, it tends to clump and produces palpable nodules. In one study, post-injection cellulitis was observed at a frequency of 1.7%.70 However, granulomas also occur with a higher frequency in elderly women.71 They consist of tightly packed, dark bluish

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**Fig. 5** Poly-L-lactic acid (Newfill [Dermik Laboratories, Berwyn, PA]) was injected too superficially and in a thin skin giving rise to a palpable and visible nodule (Courtesy: P. André, France).

**Fig. 6** Granulomas and nodules due to poly-L-lactic acid (NewFill) (Courtesy: F. Bruyns, the Netherlands).

**Fig. 7** (A) Granuloma formation due to poly-L-lactic acid (PLL) (NewFill). There are mainly epithelioid and foreign body giant cells. The latter often engulfed crystalloid PLL particles. Hematoxylin-eosin (HE), ×200 (Courtesy: F. Bruyns, the Netherlands). (B) High magnification of a PLL granuloma. HE, ×400. (Courtesy: F. Bruyns, the Netherlands).
microspheres with a diameter of 25 to 40 µm and giant cells. The nodules were shown to rapidly decrease after fractional CO$_2$ laser treatment. Recently, a grade 3 systemic reaction was observed 30 minutes after injection of CHA vocal cord filler prompting the authors to recommend a 30-minute postprocedure observation period.

**Polyacrylamide Gel**

PAAG is a suspension of 2.5% to 5% PAAG in sterile water. It is marketed under many different names: PAAG (Sinocos Eastcos, Hong Kong, China), Amazing gel, Aqualift, Aquamid (Contura International, Søborg, Denmark), Argiform, Bioformacryl, Formacryl, and Outline, which are slightly different in minute additional components. The material is widely resistant to enzymatic degradation and phagocytosis. The particles can harbor bacteria on their surface and give rise to late infections, biofilms, and abscesses. It is claimed not to induce allergic reactions or to interfere with the hemodynamic system. It can hold 300 to 400 times its weight in water. It was widely used for breast augmentation in Eastern countries. The results are immediate and overcorrection is necessary. Its major advantage is that it remains soft and pliable after injection. However, the products should not be injected over other ones. PAAG is generally well tolerated, but severe adverse effects have also been described, for example, swelling, lumps, abscesses, facial disfigurement, gel dislocation, and respiratory distress. Breast deformity, lumpiness, intermittent swelling, pain, and gel extrusion were observed in other series. The gel is exceedingly biocompatible and thus an excellent medium for bacteria. The main risk is infection frequently developing after 8 to 12 months or even later, but cultures often remain negative and only polymerase chain reactions could identify the bacteria that are normally not pathogenic, such as *Propionibacterium acnes*, *Streptococcus oralis* and *mirabilis*, *Staphylococcus aureus*, and some atypical mycobacteria. Histopathology shows foci of neutrophils and karyorrhectic material, numerous macrophages, and foreign body giant cells around a gel that appears somewhat similar to HA. Often giant cells contain vesicles full of PAAG and the material frequently shows small empty blebs both in the giant cells as well as when present in large lakes (Fig. 8). PAAG is positive with Alcian blue and not birefringent.

**Polyalkylimide Gel**

Polyalkylimide gel 4% in water (Bio-Alcamid, Polymekon, Milan, Italy) is another large volume filler to be injected into the deep dermis or under the dermis. A thin collagen capsule forms after injection preventing migration and keeping it apart from the surrounding tissue. Aspiration or punching a small hole over it permits its removal. Adverse effects were edema, bruising, nodules, infections, severe inflammatory reactions, migration despite the capsule-like fibrosis around it, unsatisfactory appearance and late-appearing abscesses. Migration is a rare event. Histopathology shows basophilic amorphous material surrounded by neutrophils and erythrocytes. Gram stain may reveal bacteria. The infections are very difficult to treat and require high-dose long-term antibiosis, incision, drainage, and irrigation.

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**Fig. 8** (A) Granulomatous reaction to polyacrylamide gel in the deep dermis and adjacent cutaneous fat. Hematoxylin–eosin (HE), original magnification ×4. (B) Granulomatous reaction to polyacrylamide gel. HE, original magnification ×10. (C) Granulomatous reaction to polyacrylamide gel. The polyacrylamide gel (PAAG) is seen as a faintly basophilic amorphous substance, but there are also empty spaces resembling fat cells. HE, original magnification ×20. (D) Granulomatous reaction to polyacrylamide gel. The giant cells contain PAAG with small blebs in it. HE, original magnification ×40.
Polyvinyl Hydroxide Microspheres in Polyacrylamide Gel
This filler is a suspension of 6% polyvinyl hydroxide microspheres in 25% PAAG hydrogel (Evolution). It is apparently well tolerated though it is not often used.\(^9\),\(^8\)

Acrylic Hydrogel
A suspension of ethyl methacrylate and hydroxyethyl methacrylate particles in HA was marketed under the brand names of DermaLive and DermaDeep. Initially reported as being well tolerated,\(^8\) it soon turned out that this biphasic filler caused late granulomas in a very high percentage of cases\(^8\),\(^7\)–\(^9\) so that it had to be withdrawn from the market. However, granulomas still occur.\(^9\) They usually present as nodules that are first palpable and then often become visible (Fig. 9). Fistulation may develop, and even a keratoacanthoma-like appearance was seen.\(^9\) The granulomas are well delimited and relatively easy to remove surgically; however, new granulomas often develop. Other treatments are intralesional corticosteroids, allopurinol, and 5-fluorouracil. Antibiotics have to be given before if an infection is suspected.\(^9\) Histopathology shows a dense granuloma with a fibrous pseudocapsule containing masses of crystalloid acrylate particles. The granulomas are made up of epithelioid and foreign body giant cells that try to engulf the particles. Some areas become necrotic and contain cholesterol clefts. Epidermal ridges may grow down and try to surround the foreign material giving rise to fistula formation. Some granulomas may become sclerotic with time (Figs. 10 and 11).

Polyacrylamide
Artecoll, Artefill, and Artesense are PMMA beads suspended in bovine collagen. Testing of bovine collagen is necessary before use to avoid an immune reaction. Individuals with a history of keloids should not be treated.\(^9\) Approximately 3 weeks after injection, the body starts depositing own collagen around the microspheres, which get virtually encapsulated by own collagen. Overcorrection is not performed. Artefill has polished microbeads being thought to attract fewer impurities and thus being less prone to induce granuloma formation.\(^9\) Metacrill and Metrex are also PMMA particles though not round and polished. Although granulomas are rare with 0.01% reported\(^9,\)\(^9\) they do occur and are difficult to treat.\(^9\) Lumps often form, particularly in the lips, but most are just palpable and not visible. Granulomas may develop several years after the injection.\(^9\) Granuloma precipitation occurred many years after injection when a patient was treated with interferon because of hepatitis C\(^9\) or laser skin resurfacing was performed over the area of injection (D. Vochelle, MD, personal oral communication). The granulomas appear suddenly with induration, swelling, tenderness, and erythema (Fig. 12). Histopathology shows a typical granuloma with round empty-appearing clear spaces in a fibrotic tissue. Treatment was performed with intralesional corticosteroids and 5-fluorouracil\(^10\) as well as allopurinol and surgery. Metacrill granulomas were melted with high-frequency “endoacagulation” leaving a residue of burnt plastic with a characteristic smell.\(^10\) Intralesional laser treatment is another option. Profil\(^\circ\) may cause considerable lipodystrophy (Fig. 13).

Paraffin and Other Mineral Oil and Lipid Derivatives
Crude substances such as vaseline, paraffin, lanolin, cod liver oil, or beeswax were used in the late 19th and early 20th century. Despite initial satisfying results, long-term results were usually appalling because of skin hardening, swelling, granuloma formation, ulceration and fistulation, infections, abscesses, and even cancer development.\(^1\)

Paraffin is irreversible and no longer legally used as a filler although highly inflammatory granulomas after fraudulent use of paraffin or other oils containing vitamin E, sometimes also vitamins D and A, are still seen (Fig. 14).\(^10\) Injection of paraffin into the penis caused sclerosing lipogranuloma characterized by fibrosis and deformation.\(^10\) Histopathologically, the deep reticular dermis and subcutaneous fat are involved with a predominantly lobular panniculitis with a Swiss cheese appearance. The cystic spaces are surrounded by foamy histiocytes and giant cells. The collagen bundles inbetween are sclerotic (Fig. 15).

Vaseline and other mineral oils cause a very similar reaction.\(^10\)–\(^10\)

Whether ultrasound liquefaction of the fat where the inappropriate substance had been injected, and subsequent
extraction by a suction cannula helps to eliminate this material remains to be seen.

Silicone
Silicone is another irreversible filler. It is a highly polymerized hydrophobic oil (Silikon 1000 [Alcon Labs, San Diego, CA], Adatosil 5000 [Bausch & Lomb Surgical Inc., San Dimas, CA], Biopolimero), gel (MDX 4–4011), or solid rubber consisting of dimethyldiisoxane units. Silicone is generally well tolerated, but the occasional adverse effects may be dramatic and irreversible; this is the reason why it is banned for cosmetic use both in the European Union as well as the United States. Those still using silicone off-label claim that pure silicone and proper microdroplet technique prevent adverse effects, but this is not generally accepted. Medical grade silicone oil is pure and sterile (►Fig. 16). The secret of good long-term results appears to be the injection of truly minute amounts. Adverse effects are local and systemic. Minor complications are small nodules seen within a year after injection and are mainly due to too much substance. However, indurations and erythema with swelling are silicone granulomas that often only appear 2 to 12 years after injection. The differentiation between siliconoma, which consists almost exclusively of macrophages containing small droplets of silicone oil and contains virtually no inflammatory cells, and silicone granuloma with silicone containing macrophages, lymphocytes, and giant cells is somewhat artificial. Both respond to intraleisonal corticosteroids in most cases. Major complications are systemic with pneumonia, acute respiratory distress syndrome, sudden death after intravascular injection, migration of large volumes of low-viscosity silicone oil, erysipelas-like reactions, blindness, loss of neurologic functions, and death after silicone oil had been inadvertently injected into the ophthalmic or meningeal vessels.

Silicone Elastomer Particles (Bioplastique)
A silicone elastomer suspension in polyvinylpyrrolidone Plasdone hydrogel was mainly used in urology and for vocal cord augmentation. It was shown to produce both lumps and granulomas.

General Features of the Histopathology of Adverse Filler Effects
Many fillers have a specific morphology and/or staining pattern in the skin. This is both true for acute reactions when the filler is still visible as well as for late reactions such as granulomas and infections with abscesses.

Bovine collagen is seen as a dense eosinophilic mass in the skin. It is not birefringent in contrast to human collagen fibers. Early “allergic” reactions usually show a lymphocytic infiltrate, which may turn into a granuloma with many epithelioid cells and some intermingled giant cells.

HA may sometimes be seen in the skin as a more or less structureless basophilic substance, this may correspond to the Tyndall effect when localized very superficially. Granulomas were relatively frequently seen in the early times of manufacturing of streptococcal HA, most probably due to the content of protein. This is nowadays very rare with this product. Another new brand caused many granulomas and abscesses. They consisted of a dense lymphocytic infiltrate with many giant cells, often of excessive size, as well as many eosinophils around basophilic HA. In case of abscesses and fistulation, foci of neutrophils are seen.

Matridex (biopolymer, Siershahn, Germany) shows both HA as well as dextranomer beads in a cell-rich granuloma. The microspheres are perfectly round and darkly basophilic or purple allowing the product to be identified.
PLL acid is seen as crystalloid material in epithelioid cell granulomas with giant cells often surrounded by fibrosis. The material is birefringent permitting its exact identification.

Acrylic hydrogel mainly causes late granulomas and no HA is seen any more. The acrylic particles are polyhedral and seen in a dense granuloma with giant cells, many of which try to engulf the foreign bodies. Necrotic areas are frequent and often contain cholesterol clefts. Clinically visible fistulae correspond histopathologically to epidermal ingrowths also trying to engulf and transepidermally eliminate filler material.

Polymethyl methacrylate (Artecoll and Artefill) is seen as round empty-appearing spaces in a fibrotic tissue. Although appearing to be of relatively uniform size this depends on the section plane. In case of granuloma formation, epithelioid and giant cells are seen in addition.

**Fig. 11**  (A, B) HEMA granulomas 2 years after injection. (C) Some granulomas extirpated from the perioral region. (D) Histopathology of HEMA nodules shows well-delimited granulomas surrounded by a fibrous pseudocapsule. Hematoxylin–eosin (HE) stain, scanning magnification, ×4. (E) HEMA granuloma. There is a dense granulomatous infiltrate with epithelioid cell, some giant cells, many HEMA particles, which stand out by their polygonal appearance, and sinus and fistulae tracks, the latter also containing HEMA particles. HE, ×100. (F) Higher magnification of the vicinity of a sinus with many HEMA particles, monstrous giant cells, and neutrophils. HE, ×200. (G) HEMA granuloma with particles and many slit like, so-called cholesterol clefts. HE, ×200. (H) HEMA granuloma during treatment with intralesional triamcinolone acetonide plus 5-fluorouracil. There is little infiltrate and the connective tissue appears hyalinized. HE, ×200.

**Fig. 12**  Granuloma due to polymethyl methacrylate microspheres in collagen (Artecoll) (Courtesy: F. Bruyns, the Netherlands).

**Fig. 13**  Late complication of Profill demonstrating serious fat atrophy after initial inflammation. (Courtesy: P. André, France).
PAAG is very well tolerated biologically. The main risk is infection that may cause abscesses and necroses. Granulomas show epithelioid and giant cells. The material is basophilic and does not exhibit a wavy structure often seen with HA.

Silicone oil causes granulomas with droplets of varying size, some of which are seen in epithelioid cells. Giant cells are rare as there are no particles. Often dense lymphocytic infiltrates are seen in perivascular localization.

Sclerosing lipogranuloma is a characteristic feature of paraffin injection, mainly in the penis to increase its girth. It is characterized by a Swiss cheese like aspect in a fibrotic tissue with lymphocytes, epithelioid, and giant cells. The empty spaces are of variable size.

The injection of vitamin E in different oils gives a similar histopathological picture, but as these injections are now mainly made in the face, particularly in the lips, by nonmedical persons the changes are much more acute and the inflammatory component is more obvious in these cases.

### Imaging Techniques

Several imaging techniques were applied to aid in the diagnosis of filler complications, particularly in the diagnosis of suspected abscesses. Further indications are overfilling, migration, foreign-body granulomas, and scarring.\(^{117}\) Using high-frequency ultrasound complemented with magnetic resonance imaging (MRI) and white blood cell scintigraphy, allowed the distinction between infections, fibrosis, granulomatous inflammation, and product migration.\(^{118}\) Calcium hydroxyapatite is radio-opaque and can be seen in normal radiographs;\(^{119}\) however, its injection may cause local hypermetabolism and thus be a source of false-positive findings in positron emission tomography scans.\(^{120,121}\) Using conventional X-ray films, computed tomography, and MRI techniques, a distinction of different materials frequently may be feasible.\(^{122}\)

### General Treatment Remarks

Prevention is always better and easier than treatment—this rationale is also true for filler adverse effects. After identifying the exact nature of an adverse effect, the appropriate therapy has to be chosen. Early adverse effects such as injection pain, immediate swelling, and edema usually do not require specific treatment. Cooling is often sufficient to alleviate the immediate postinjection pain; however, this is rarely seen anymore as more and more preparations contain a local anesthetic. Swelling may respond to acetylsalicylic acid (Aspirin [Bayer, Leverkusen, Germany]) or another nonsteroidal anti-inflammatory drug. Placement of too much material or in the wrong area requires immediate massage or removal, if possible. Lump formation after calcium hydroxyl apatite injection in the lip is a technical fault as well as too superficial an injection. Proper training before starting to inject is mandatory.

Blanching extending beyond the immediate area of the injection volume may be a sign of vascular occlusion. Nitroglycerin cream and warming may be sufficient in mild cases.\(^{13}\)

HA can de-dissolved with hyaluronidase. Most preparations are of animal origin and there is the theoretical possibility of a sensitization. It is wise to use one preparation to get experience with it as the dosage may vary among the different drugs. The effect is usually seen within hours, and
reinjection is possible after 24 hours, so small doses are recommended in the beginning.

The problem is the treatment of late and delayed adverse effects. First, the responsible substance has to be identified. This is often impossible as the patients do not know, or are reluctant to disclose, which filler had been injected. Once a granuloma has developed it is to be assumed that granulomas will continue to develop as long as the foreign material is in the skin. Whether attenuated total reflectance/Fourier transform infrared analysis spectroscopy really allows fillers to be reliably identified remains to be seen. Another validated method is the histological examination of sections, which yield quite specific changes with most different fillers.

The differentiation of infection from noninfectious granulomas is possible with radioactive labeled leukocytes. In case of infection, antibiotics have to be given long enough and in doses capable of containing the infection. Staphylococcus fast antibiotics such as cephalosporins are given intravenously. Vancomycin (Pfizer, Munich, Germany) is administered for Staph epidermidis.

Granulomas often respond to an intralesional injection of a mixture of 250 mg 5-fluorouracil/mL, 10 mg triamcinolone acetonide/mL plus mepivacaine 1 mL, which is given first twice, then once weekly, plus allopurinol 300 to 600 mg/d. Tumor necrosis factor α inhibitors have not yet gained much acceptance in the treatment of granulomas. In progressive cases where all conservative treatment options fail, surgical removal may be inevitable.

**Conclusion**

Fillers belong to the most frequently used substances in esthetic medicine. The “consumers” are not sick patients, but they are healthy persons expecting to look better after the procedure. Any adverse effect, whether immediate, late or delayed, temporary or irreversible, is a catastrophe for them and potentially for the treating physician. All measures have to be taken to avoid them: The physician must be well trained, use the best product, respect indications, contraindications, proper aseptic injection techniques, and adequate localization for each specific filler. The patient has to follow the physician’s recommendations after treatment. The best would be to give a “filler pass” to the patient that notes which filler was when and where injected. Despite all precautions, adverse effects may occur. Take them seriously and never dismiss a patient’s concerns. Treatment should be instituted as soon as possible.

**References**


**Fig. 16** Siliconoma. (A) Perivascular lymphocytic infiltrates and an edematous reticular dermis. Methylene blue stain × 100. (B) There are dense perivascular lymphocytic infiltrates and some relatively small, round, empty-appearing spaces. Methylene blue stain × 200. (C,D) The connective tissue is very loose with many barely visible round spaces that are smaller than normal fat cells. Cresyl violet (C) × 100, (D) × 200.
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Complications of Collagen Fillers

Patricia Lucey, MD1    David J. Goldberg, MD2,3

1 Department of Dermatology, Albert Einstein College of Medicine/Montefiore Medical Center, New York, New York
2 Skin Laser and Surgery Specialists of NY/NJ, New Jersey
3 Department of Dermatology, Mount Sinai School of Medicine, New York, New York


Abstract

As the skin ages, a deficiency in collagen occurs, thus injectable collagen products have become a sensible and popular option for dermal filling and volume enhancement. Several types of collagen have been developed over the years, including animal sources such as bovine and porcine collagen, as well as human-based sources derived from pieces of the patient's own skin, cadaver skin, and later cultured from human dermal fibroblasts. While collagen overall has a relatively safe, side effect profile, there are several complications, both early and late onset, that practitioners and patients should be aware of. Early complications, occurring within days of the procedure, can be divided into non-hypersensitivity and hypersensitivity reactions. The non-hypersensitive reactions include injection site reactions, discoloration, maldistribution, infection, skin necrosis, and the very rare but dreaded risk of vision loss, whereas the hypersensitivity reactions present usually as delayed type IV reactions, but can also rarely present as an immediate type I reaction. Late complications, occurring within weeks to even years after injection, include granuloma formation, foreign body reactions, and infection secondary to atypical mycobacteria or biofilms. This review will give a detailed overview of the complications secondary to cutaneous collagen injections.

History of Collagen Fillers

Collagens constitute approximately one-third of the body's own structural proteins. They are the major structural component of the normal human dermis and are responsible for the skin's strength and support. In normal adult skin, the dermal matrix is composed of 80% to 85% of type I collagen, 10% to 15% of type III collagen, in addition to glycosaminoglycans and elastin fibers. Type I and type III collagens are synthesized by dermal fibroblasts as α-pro-collagens, which then undergo subsequent hydroxylation, followed by triple helix formation. Type I collagen is composed of two α-1 and one α-2 chains, whereas type III collagen is composed of three α-1 chains. This triple helix structure is then secreted into the extracellular space, where proteinases cleave the terminal domains, after which these final collagen molecules assemble to form fibrils with other noncollagen molecules.1

As the skin ages, there is a decrease in collagen production by fibroblasts, resulting in an overall 20% decrease in dermal thickness, as well as thickened, fragmented, and irregular collagen bundles.2 Furthermore, exposure to ultraviolet radiation has been shown to increase the level of matrix metalloproteinases, including collagenase, which increases collagen degradation.3,4 Therefore, because of this obvious defect and deficiency of collagen in the aging skin, using collagen as a dermal filler was obvious and gained popularity.

First Uses of Collagen

In the 1970s, animal- and human-derived collagens were studied for soft tissue augmentation.1 Fat was the first dermal filler approved by the Food and Drug Administration (FDA), and collagen was the second, approved over three decades...
ago in the 1980s. The sources of collagen were originally bovine, but then later they were derived from the patient’s own skin and cadaver skin. Finally, collagen has been cultured from both human dermal fibroblasts, and porcine tissue.

In 1977, clinical trials on the original bovine collagen filler were performed. This collagen was composed of 95% type I collagen and 5% type III collagen.\textsuperscript{1,5} Zyderm I (McGhan Medical Corporation, Fremont, CA) was ultimately FDA-approved in 1981 and was composed of bovine collagen (35 mg/mL), while Zyderm II (McGhan Medical Corporation) was FDA approved in 1983 and was composed of bovine collagen (65 mg/mL). Both were buffered in a saline solution with 0.3% lidocaine. Zyplast (McGhan Medical Corporation) was FDA approved in 1985 and was composed of bovine collagen cross-linked with glutaraldehyde, which results in less immunogenicity and a longer lasting effect than Zyderm.

Later, combinations of bovine collagen products appeared with Arteplast (Artes Medical Inc., San Diego, CA; discontinued), Artecoll, Artfill, and Resoplast, all being a combination of bovine collagen and inert polymethyl methacrylate (PMMA) beads and 0.3% lidocaine. Of note, the PMMA microspheres available today are not absorbed by the body and therefore provide a permanent filler option. Furthermore, these microspheres act as a matrix, stimulating the patient’s own fibroblasts to produce collagen and encapsulate each microsphere. All bovine-based collagen fillers have the risk of causing an allergic hypersensitivity reaction; therefore, two consecutive skin tests are recommended at least 1 month before the treatment.\textsuperscript{1,5,6}

Later, human tissue matrix collagen was cultured using large pieces of the patient’s own skin (Autologen, Collagenesis Corp.), using punches of the patient’s own skin (Isolagen), and cadaver skin (Dermalog, AlloDerm, and Cymetra). Autologen and Dermalog are no longer available. Finally, human-based collagen implants came out and were approved by the FDA in March 2003, and included CosmoDerm (INAMED Corporation, Santa Barbara, CA) I, CosmoDerm II, and CosmoPlast. These human-based collagens contained types I and III human collagen and were cultured from human dermal fibroblasts harvested from bioengineered human skin cells, and cultured in a bioreactor simulating the human body, causing secretion of collagen and extracellular matrix proteins. CosmoDerm I contains 35 mg/cc human-based collagen dispersed in a phosphate-based saline solution and 0.3% lidocaine, and CosmoDerm II contains about twice as much concentration as that found in CosmoDerm I. CosmoPlast is similar to CosmoDerm I, but it is cross-linked with glutaraldehyde, making it more resistant to degradation. Unlike bovine-based collagen fillers, no skin testing is required for any of the human-derived collagen products.\textsuperscript{1,5}

Of note, after bovine- and human-based collagen fillers appeared, newer porcine-derived collagens came out in the market. However, none are currently available in the United States for dermatological use. Porcine collagen is temporary and biodegradable and has a duration in the tissue of around 12 months. Evolence (Johnson & Johnson; discontinued) and Evolence Breeze are porcine collagen gel implants composed of 3.5% homogenous type I collagen extracted from porcine tendons and suspended in phosphate-buffered saline and then cross-linked through its patented Glymatrix Technology using the natural sugar, D-Ribose. As this proprietary technology does not involve the use of chemical cross-linking agents, it supposedly eliminates all potentially antigenic compounds that might induce allergic reactions, and thus no pretreatment of the skin was required.\textsuperscript{7} While it had an excellent safety record, and unlike bovine collagen was never associated with a single allergy, Evolence products were withdrawn from the U.S. market in 2009 by the manufacturer, only 1 year after being approved. The reason for this withdrawal was most likely because of a highly competitive market for other non-animal-based dermal fillers, and because historically porcine products have not done well as many other laboratory-grown products. Other porcine collagen dermal filler products include Fibroplast (Aspid, Mexico, D.F., Mexico), which is no longer being marketed in the United States, and Permacol, which is now only being used in the United States as a mesh or implant for surgical repairs.\textsuperscript{7}

Several studies have been performed on bovine-, porcine-, and human-derived collagen, validating their efficacy for soft tissue augmentation and are now recognized as a well-accepted treatment modality for many cosmetic purposes. However, several studies and reports have shown risks of both early and late complications to collagen-based fillers, which will now be discussed in detail.

**Early Complications**

Early complications to collagen-based fillers occur immediately up to several days after treatment, and can be divided into non-hypersensitive and hypersensitive reactions.

**Non-Hypersensitive Reactions**

**Injection Site Reaction**

The most common non-hypersensitive reactions, which can occur with any filler, are local injection site reactions, which can be manifested as erythema, edema, pain, tenderness, bruising, or itching (\textsuperscript{1,8,9} Figs. 1 and 2). Patients need to be informed of the high likelihood of these reactions, because most fillers usually result in some degree of injection site reactions. Erythema and edema is usually temporary and resolves within a day, whereas deeper swelling and bruising usually resolves within 4 to 7 days. Swelling and bruising can be attenuated by avoiding aspirin-containing compounds and anticoagulants (provided the patient’s primary physician or cardiologist approve), nonsteroidal anti-inflammatory drugs, and various vitamin supplements such as vitamin E, ginger, ginseng, ginkgo biloba, garlic, kava-kava, celery root, fish oils, 7 to 10 days before the procedure.\textsuperscript{1,8,9} Non-hypersensitivity type inflammation is mediated by vasodilation, increased vascular permeability, and migration of inflammatory mediators, and can occur during the injection process, manifesting as minor reactions of erythema, induration, erythema, and itching, and can occur regardless of negative testing for allergy to bovine collagen.\textsuperscript{9} Although these are usually short lived, reports of long-lasting erythema and itching with Artecoll has been reported. Artecoll has also been reported to cause telangiectasias at the implantation site in patients with very thin skin, but this usually disappears by 6 months.\textsuperscript{10}
Discoloration
Some early complications from collagen filler can include temporary discoloration of the skin in or around the injection site, resulting in redness, whiteness, or hyperpigmentation. Furthermore, the depth of dermal filler placement is particularly important in preventing discoloration, as injecting too superficially can cause a blue–gray discoloration known as the Tyndall effect. The high-risk areas for this Tyndall effect include the nasojugal folds, nasal dorsum, the lip, the infraorbital troughs, and fine superficial perioral and periorbital lines.

Infections
Any type of dermal filler that is injected into the lip or perioral area can trigger reactivation or herpes and thus antiviral prophylaxis is necessary in all patients with a prior history. In patients with active herpes lesions, injections should obviously not be performed until the lesions have completely resolved.

Bacterial contamination, infection, and abscess formation are another rare complication that can occur with collagen fillers. Early infections can occur up to several days to a week after injection, whereas late infections occur several weeks to months after injection, and will be discussed in more detail later. Lesions of early infection can be almost indistinguishable from an inflammatory hypersensitivity response. They may resolve spontaneously or require minimal medical intervention. Early infections from collagen injection typically become symptomatic 8 to 12 days after injection and are described as granulomatous allergic tissue reactions developing into abscesses, localized granulomatous tissue reactions, abscess-like nodules, delayed granulomatous reactions, sterile abscesses, foreign body nodules, or delayed onset reactions. Although cultures have not demonstrated consistent findings, when the culture is positive, skin flora such as *Staphylococcus epidermidis* or *aureus* predominate. Abscesses, which are fluctuant, are distinguished from a hypersensitivity reaction, which may be erythematous and indurated but not fluctuant. Abscesses can be treated with broad-spectrum antibiotics and incision and drainage but may result in scar formation.

Abscesses may also be treated with intralesional steroids, as some components of abscess formation are thought to be because of a hypersensitivity reaction, as a majority of patients with abscesses have serum antibovine collagen antibodies. The risk of infection and contamination can be minimized by cleaning the treatment area of the skin first with an antiseptic agent such as isopropyl alcohol or chlorhexidine. If an infection is suspected, it is important to try to culture any available exudate and start empiric treatment with an antibiotic such as clarithromycin until the more specific culture results become available.

Skin Necrosis
Skin necrosis is a rare but important complication that can be associated with collagen fillers. Necrosis can occur secondary from vascular occlusion by injection of the collagen directly into a vessel, or by mechanical disruption or compression of the vascular supply by the surrounding collagen placement. The majority of these cases occur in the glabella, thought to be because of less collateral circulation in the glabella, as small...
caliber vessels branch from the supratrochlear arteries to supply this watershed region. The first signs of necrosis may be immediate or delayed blanching of the injection area, followed by the appearance of dusky and then black areas, then the formation of a moist pustule, dry eschar, and later ulceration. The ulcer will eventually heal by granulation, reepithelialization, and scar formation.9,12

Several precautions can be taken to avoid necrosis. When injecting in the glabella, it is important to inject superficially and medially as to avoid the supratrochlear arteries, to aspirate before injecting, to use low volumes of products over more sessions as opposed to using high volumes over one session and to use only products that are manufactured for more superficial placement, such as CosmoDerm. When the first signs of skin of necrosis occur, immediate discontinuation of the injection is necessary followed by possibly warm compresses, massage, and tapping on the area to theoretically facilitate vasodilation and blood flow. Furthermore, the application of ice to prevent further cell death and nitroglycerin paste to further promote vasodilation has also been suggested to be of potential benefit.12–14

**Vision Loss**

The most serious and dreaded complication of collagen filler injection is vision loss. This is thought to occur from vascular occlusion of the rich arterial anastomosis of the extraorbital branches of the ophthalmic artery in the glabellar area.5 One case of blindness after Zyplast injection into the glabella has been reported,15 and there have also been two reports of irreversible unilateral or bilateral vision loss after bovine collagen injection, probably resulting from an occlusive event involving the retinal artery.16,17 There has also been a case reported of the vision loss and total ophthalmoplegia after injection of PMMA into the glabellar area.18

**Placement and Maldistribution**

Inappropirate placement of dermal fillers such as collagen is a common error and is associated with a range of complications, from the obviously visible product, to inflammatory nodules, and even hypertrophic scarring. If collagen filler is placed too superficially, this can lead to lumps, bumps, and beading of the visible product underneath the skin surface.8 Such reactions can be prevented by injected deeper, and can often be treated by simple local massage, aspiration or incision, and drainage.13 However, because collagen fillers are less viscous than other fillers, such as hyaluronic acid, they have the advantage of correcting fine lines and wrinkles better and are less likely to produce irregularities when injected superficially as compared with other more viscous fillers.7

While porcine collagen is no longer available for use in the United States, there were several reports of nodule formation developing after injection, especially when used around the lips. In one case series, 20 female patients received Evolence filler in the lips, and within 3 weeks, 16 patients (80%) experienced multiple lips nodules within 3 weeks. Many of these nodules required further treatment with collagenase, lancing and excision, and some nodules were still quite visible in six patients over 1 year later.19 However, according to the manufacturer, because Evolence was meant for injection into the mid-deep dermis, caution was advised to avoid over-correction of the vermillion border of the lip because of minimal tissue stresses at this site.

Furthermore, if the collagen filler is placed too deeply, as to the level of the peristeal plane, the periosteum can be disrupted, leading to subperiosteal hemorrhage and pain.8 PMMA is a permanent filler agent, and is now available for use in the United States as Artefill. PMMA fillers are optimally placed in the deep dermis or subdermis, but when they are placed too superficially, pruritus, redness, and rarely hypertrophic scarring may occur.8,10 Localized itching and redness can sometimes be treated with topical or intralesional steroids, whereas hypertrophic scarring can be softened with a pulsed dye laser or topical or intralesional steroids.9

**Hypersensitive Reactions**

With the exception of autologous fat and autologous collagen, all other fillers are generally composed of foreign body material, thus varying degrees of immune system reactivity and hypersensitivity can occur. These reactions can range from mild irritation and redness (− Fig. 3), to nodules and abscess, and even to anaphylaxis. Furthermore, foreign substances already on the skin, such as lipstick or makeup, could be introduced into the skin during the procedure, also causing a reaction.8,9

Bovine collagen being from a nonhuman, animal source can be immunogenic, and thus requires two consecutive negative skin tests at 6 and 2 weeks before treatment.

**Fig. 3** Presumed hypersensitivity reaction to injection.
Approximately 3% of the general population are allergic to bovine collagen and 70% of these reactions will manifest as a delayed type IV hypersensitivity reaction 48 to 72 hours of the first test. After the first negative test, the risk of allergy is between 1.3% and 6.2%, and after two negative tests the risk is 0.5%. However, exposure to the allergen during the first skin test may act as a sensitizer in 1 to 2% of the people. The allergy risk for Artecoll (PMMA spheres in partially denatured bovine collagen) is lower than that of plain bovine collagen, at a rate of 0.78%. These hypersensitivity reactions can manifest as erythema, edema, pain, tenderness, or nonfluctuant nodules. Patients should be reassured that these hypersensitivity responses to bovine collagen usually resolve within 4 to 24 months and can be treated with topical, intrallesional, or systemic corticosteroids, and topical tacrolimus and oral cyclosporine have also been used with success.

Furthermore, some patients exhibit an immediate type 1 hypersensitivity reaction within minutes or hours of the first test, which suggests that some patients already have circulating antibodies to the bovine collagen before exposure, theoretically implicating dietary exposure to beef as a factor. Type 1 hypersensitivity to bovine collagen results from the release of histamine causing vascular permeability, leading to erythema, edema, and itching. However, a more systemic reaction can occur 48 to 72 hours after injection, characterized by fever, malaise, and urticaria which can be treated with short-term oral steroids. Other more rare systemic complications such as flu-like symptoms, paresthesias or difficulty breathing, have also been described after bovine collagen injection. Furthermore, only one report of severe anaphylactic shock has been reported to bovine collagen.

In patients with bovine collagen hypersensitivity, autologous, cadaveric, and human based-dermal fibroblast-derived collagen products can be offered as they have a lower risk of hypersensitivity reaction. However, there have been two cases report of a possible hypersensitivity reaction to human-derived collagen, manifested as erythema, induration, burning, and nonerythematous subcutaneous lumps at the injection site, at 72 hours and 10 days after the injections, respectively. One patient had previously tested negative to bovine collagen, and the other patient had previously been injected with bovine collagen with no reports of any apparent hypersensitivity. Both patients were treated with topical tacrolimus and both reactions resolved over 3 to 6 weeks, respectively.

Because of possible reactions to both bovine and human collagen, however, rare they may be, adequate skin testing and the selection of fillers with a low reactivity profile is of the utmost importance. Fortunately, a localized allergic reaction to either bovine collagen or the extremely rare reaction to human collagen, generally does not produce long-term morbidity or complications, and these reactions can often be treated with topical or intrallesional steroids, antihistamines, topical tacrolimus, or systemic steroids.

**Late Complications**

Delayed complications to collagen-based fillers are those that occur anywhere from 6 weeks to years after injection and while they may have a similar presentation to early complications, many of the mechanisms behind the reactions are different.

**Granuloma Formation**

Foreign body granulomatous reaction and granulomas may occur during the first few months after bovine filler injection. These can appear as erythematous, tender subcutaneous nodules, and can result in persistent discoloration and permanent scarring. Rare cases have been reported of deep granulomas extending into the superficial and deep muscle 2 to 10 years after bovine filler injection. Early granulomas reveal an inflammatory infiltrate that surrounds the implant, with fibroplasia at the periphery of the granuloma reaction. Late granulomas are more developed and reveal a dense granulomatous inflammatory infiltrate, consisting of noncaseating granulomas with histiocytes, epithelioid cells, and multinucleated histiocytes. Interestingly, there have been two case reports of granuloma annulare occurring at the collagen test site; however, one patient had a history of granuloma annulare, thus, this reaction may have represented the Koebner phenomenon. Disseminated and recurrent sarcoid-like granulomatous panniculitis has also been described as a very rare reaction to bovine collagen injection. One report of a keratoacanthoma arising in a severe granulomatous reaction site after Zyplast injection has also been described in a 27-year-old male patient.

Bovine collagen and PMMA (Artecoll and Artefill) can also cause delayed granulomas, although the rate has been shown to be very low around 0.01%. These granulomas generally occurred 6 to 24 months post treatment, and often appeared after the second or third implantation of the product, suggesting a delayed hypersensitivity. While the cause is unknown, half of the patients reported an associated severe infection such as influenza or some type of facial injury, suggesting an immune response triggering a delayed hypersensitivity reaction. Histologically, these granulomas show a wide distance between the PMMA microspheres filled with macrophages, giant cells, fibroblasts, and broad bands of collagen fibers. There has also been one report of a patient with chronic hepatitis C on treatment with peg-interferon α-2a and ribavirin who developed disfiguring facial swelling in foci where Artecoll had been injected 10 years earlier.

It is important to note that Artefill is slightly different from Artecoll. Artefill is a newer product that is derived from a closed US bovine herd and is said to have much more consistency in the PMMA particle size, with highly uniform microspheres with less than 1% of the particles being smaller than 20 µm. Therefore, it is believed that because of the larger size and uniformity, there is a significantly less risk of ingestion of smaller particles of product by macrophages and thus a very low risk of immunogenicity and subsequent granuloma formation.

In regard to combination products of bovine collagen and PMMA, 80% of the bovine collagen is gone after 1 to 3 months, whereas the PMMA microspheres are considered permanent and persist for years. This persistence is expected to induce a mild but controlled granulomatous foreign body reaction,
with deposition of fibrous tissue, which causes the wanted prolonged filling effect.\textsuperscript{10,35} However, this filler must be injected into the reticular dermis, and if injected too superficially into the dermis is more likely to produce an evident whitish nodule or granulomatous reaction.\textsuperscript{36,37}

Treatment of these various types of collagen filler associated granulomas include intralesional steroid injections, which should be injected directly into the nodule, progressing to higher concentrations as needed every couple of weeks. However, it is important to distinguish this type of a granulomatous nodule formation from superficial beading and ridging that represents a hypertrophic scar because of too superficial placement of PMMA as these may require excision or laser.\textsuperscript{8,9} Interestingly, there has been one case report of an Artecoll-induced granuloma responding positively to allopurinol,\textsuperscript{38} and another Artecoll-induced granuloma responding to intralesional 5-fluorouracil injections.\textsuperscript{39}

**Infection**

Infection and abscess formation is a rare complication of collagen fillers and can occur early on or can be delayed, several weeks to months after injection. Infections that develop more than 2 weeks post procedure are more likely to suggest an atypical mycobacterial infection. Patients may present with a firm, slightly tender mass or nodule with or without fluid, and they may also have systemic reactions, including fever, leukocytosis, weight loss, and fatigue. Lesions should be aspirated or biopsied for tissue culture, and up to 4 antimicrobial agents may be used if the infection is mycobacterial. Surgical removal of the lesion may also speed recovery.\textsuperscript{11}

Aseptic abscess and cyst formation is another rare adverse localized reaction that can occur after collagen filler. The abscess is technically “sterile,” meaning negative culture, and can be confined to the injection site or extend to adjacent tissue. Histologically, there are numerous neutrophils, lymphocytes, plasma cells, and multinucleated giant cells surrounding particles of injected collagen, cellular debris, and hemorrhage.\textsuperscript{6,12}

Infection or contamination by a tainted product is another issue that could potentially occur with the use of collagen fillers, especially those not approved by the FDA. While no reports of tainted collagen fillers have been reported, in 2002 there was an outbreak of *Mycobacterium abscessus* infection in New York City following soft tissue augmentation with an unapproved hyaluronic acid product, which was eventually traced to tainted product smuggled from Venezuela and injected by nonphysicians.\textsuperscript{9,11,40} Therefore, when choosing any collagen-based filler, it is best to choose products approved by the FDA and from trusted distributors.

Another important infectious topic to discuss is the role of biofilms (\textsuperscript{Fig. 4}). Biofilms are a structured and complex collection of microorganisms encapsulated within a self-developed polymeric matrix and irreversibly adherent to a living or inert surface. Biofilms have impaired immune system penetration, reduced growth rates and susceptibility, and produce substances that individual bacteria are unable to produce alone. Biofilms excrete a protective and adhesive matrix which may interfere with macrophage phagocytosis and biofilms also allow for up to 1000 fold improved resistance to antibiotics. As biofilms progress, they become more antibiotic and culture resistant, and once biofilms are established, they are extremely difficult, if not impossible, to completely eradicate. Current culture techniques fail to identify biofilms and frequently, the bacteria are not found in clinically infected abscesses and will result in an abscess being labeled as “sterile.”\textsuperscript{41,42}

Regarding the topic of collagen, all fillers, except autologous fat, are composed of foreign materials and thus can serve as a potential source for biofilm formation and biofilm-related soft-tissue filler complications. In fact, many experts believe that many of the side effects of fillers are caused by biofilms, but that these infections are difficult to culture and thus prove. Biofilms represent a low-grade smoldering infection with a low response from the host, and they live in a dormant state. However, an active infection or granulomatous response can be triggered by dental manipulation, injection into the skin as with soft tissue fillers, or any other trauma. When associated with fillers, biofilms have been suggested to play a role in the development of delayed foreign body granulomas, the activation of quiescent granulomas, abscess, recurrent local infections, and even systemic infection.\textsuperscript{13,41–43}

Prevention of biofilms can be done by following aseptic technique, using smaller gauge needles to minimize trauma and limit access for bacteria, avoiding makeup application immediately before and after injection, and not injecting during active acne or any other skin infections. It should also be noted that the lips may actually be the highest risk area for potential biofilm introduction during collagen filling because of the proximity of the oral flora with its multitude of bacteria.\textsuperscript{42} Furthermore, because of the well-recognized risk of biofilm formation around orthopedic implants bonded with PMMA,\textsuperscript{44} patients treated with bovine collagen and PMMA combination fillers such as Artefill, should be carefully assessed for the formation of biofilm complications.

Treatment involves culturing and draining any fluctuant areas and immediately starting any systemic antibiotics even if the culture is negative. The antibiotic regimen should consist of at least two drugs, such as a quinolone and a
third-generation macrolide, to prevent further biofilm deposition. Of note, macrolides have been shown to accumulate in the subcutaneous fat, where much of the filler material and related biofilm resides, and thus have been shown to be quite effective. Only after a trial of antibiotics, should intravenous high-dose steroids be considered, and if all else fails, excision of the filler can help get rid of the biofilm.

**Trigger of Autoimmune Syndromes**

In 1993, there was a study published addressing the association between bovine collagen injections and a dermatomyositis or polymyositis-like syndrome. A total of 8 patients with dermatomyositis and 1 patient with polymyositis were identified from approximately 345,000 patients who received injectable bovine collagen implants. These nine patients were diagnosed an average of 6.4 months after collagen exposure, either by injection or skin test. Eight of the nine patients had a delayed-type hypersensitivity response at the test and/or treatment sites, and five of six patients tested were found to have increased serum antibodies to bovine collagen. Compared with the general population, the incidence of dermatomyositis or polymyositis among bovine collagen-treated patients was found to be statistically increased.

However, as this study was done, several retrospective studies have found no evidence to suggest that bovine collagen induces connective tissue disease in humans. In some of these studies, sera were collected from patients who developed erythema or induration at the intradermal test or treatment sites, and were evaluated for antibodies to bovine dermal collagen. While elevated levels of antibovine collagen antibodies were present in several patients and did correlate significantly to localized responses at injection sites, systemic complaints could not be correlated with either skin reactions or antibody titers. Therefore, immune responses to bovine collagen were thought to be typically only localized reactions. Furthermore, these antibovine collagen antibodies did not cross-react with human dermal collagen, and in the sera of these patients there were not any antibodies found against human types I, II, and III collagens nor did they have elevated circulating immune complexes. Other studies showed that when comparing incidence rates, there was a consistent finding of fewer than expected dermatomyositis and polymyositis cases among bovine collagen users as compared with the number of cases expected in a model of the bovine collagen-treated population, matched for age, sex, and race.

**Conclusion**

Over the years, many other types of dermal fillers have become available, many of which have several advantages over collagen such as no need for skin testing and longer lasting effects. While these newer dermal fillers have gained popularity and are more frequently used than collagen, many practitioners are still relying on collagen for soft tissue augmentation. While the overall safety profile of collagen is excellent, both the early onset and late onset complications should be fully appreciated to forewarn patients for their potential risk as well as to better understand how to manage these complications should they arise.

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**References**

Management of Complications of Injectable Silicone

Doris Hexsel, MD1,2  Marina Resener de Morais, MD1

1 Brazilian Center for Studies in Dermatology, Porto Alegre, RS, Brazil
2 Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, RS, Brazil

Address for correspondence Doris Hexsel, MD, D. Pedro II 1592, 90550–141, Porto Alegre, RS, Brazil (e-mail: doris@hexsel.com.br).


Abstract

Soft tissue augmentation is a common procedure, and a wide variety of injectable fillers are used. Liquid injectable silicone (LIS) was the first highly popularized injectable filler. LIS is a permanent filler and can be used in the correction of facial furrows and wrinkles. Some complications are inherent to the procedure and can resolve spontaneously, such as redness, swelling, and immediate hypersensitivity reactions. Unintended reactions, such as granulomas, infections, vascular occlusion, can also follow the treatment with LIS and may appear several years after the injections. These can be difficult to manage, show little or no tendency to spontaneous resolutions, and rarely resolve completely. Injecting physicians must be aware of these potential complications caused by LIS because early medical care and treatment, including psychological support for these patients, can minimize the consequences for patients and physicians, and may also help obtaining better outcomes when treating complications.

Keywords

► dermal fillers
► injectable augmentation
► silicone
► complications

Soft tissue augmentation is a common procedure for which surgical techniques, such as subcutaneous incisionless (subcision) surgery using needles to make subcuticular cuts as well as a wide variety of injectable fillers are used.1

Liquid injectable silicone (LIS) is a colorless and odorless product, composed of long chains of polymerized dimethylsiloxane and was the first highly popularized injectable filler2 used for permanent soft tissue augmentation.3 LIS applies to the same indications as other fillers. It can be used in the correction of facial furrows and wrinkles.4 However, some authors do not indicate its use for lips because all permanent fillers promote some fibrosis around the implant, leaving the skin with a harder than normal consistency. LIS is contraindicated in patients with chronic inflammatory diseases, those with multiple allergies, and in patients who suffer from infectious processes in close proximity to the injected sides. They may thus be at a greater risk for inflammatory complications following silicone injections.5,6

All injectable fillers may produce various unintended reactions, ranging from minor and self-limited responses to severe complications.5 Nonpermanent agents may induce severe complications, but these are likely to resolve spontaneously in a variable period of time. Permanent fillers can also evoke milde-to-severe adverse reactions, but the latter show little or no tendency to spontaneous resolution. They may appear several years after the injections, when sometimes the patient does not remember which product was used.7 For this reason, it is of particular importance to record the previous fillers that were used by each patient, not only in the patient’s chart/medical record, but also in an “injectable patient passport.”

Dermatologists and aesthetic surgeons must understand the potential complications caused by LIS and other permanent injectable fillers, as well as be confident in managing the entire spectrum of adverse sequelae. Some complications of filler injections are technique-related, but complications of permanent fillers can also last longer or remain permanently. The classification of dermal fillers complications8 is also applicable for LIS, and is displayed in ►Table 1.

In this article, the authors will discuss complications that can be seen after silicone injections and their management. In any case, patients deserve care and physicians’ attention.
Main Complications Inherent to the Procedure/Minor or Early Complications with LIS

Dyschromias
Dyschromia may occur after silicone injections, staining the skin yellowish-brown.\(^4,9\) It may result of superficial injections of significant amounts of this filler. It can be prevented with proper injection technique, avoiding silicone deposition especially in thin skin.

Hyperpigmentation can appear as a result of hemosiderosis, resulting from hematomas. It can also be due to post-inflammatory hyperpigmentation\(^10\) which occurs in prone individuals following any kind of aggression to the skin, being aggravated to subsequent exposure to the sun.\(^9,11\)

Overcorrection
This is another totally technique-dependent complication and results in small nodular elevations, usually in the first 12 months following application. It is caused by implantation of excessive volumes\(^4,9\) or at the incorrect depth and more frequently occurs in areas of fine and easily distended skin such as the periorbital wrinkles (→ Figs. 1 and 2). An exaggerated proliferative fibro-histiocytary response occurs when silicone is injected at the papillary dermis, and may result in skin relief alterations.\(^11\) Other common surface deformities include intentional overcorrections.\(^11\) Asymmetry and distortion can occur if the injecting physician does not pay attention to the volumes implanted. These should be prevented, as they are difficult to treat. In some cases, surgical interventions to remove the excessive filler can be considered.

Immediate Hypersensitivity Reactions
Most injectable fillers often result in some degree of injection-site-related swelling or bruising for 4 to 7 days. Swelling can often be minimized by avoiding aspirin compounds, nonsteroidal anti-inflammatory drugs, and many vitamin supplements (vitamin E, ginger, ginseng, ginkgo biloba, garlic, etc.).

Table 1 Classification of dermal fillers complications

<table>
<thead>
<tr>
<th>Minor complications/usually early</th>
<th>Major complications/usually late</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inherent to the procedure</td>
<td>Technique-related</td>
</tr>
<tr>
<td>• Erythema, redness</td>
<td>• Surface deformities: excessive elevation, persistent overcorrection, nodules</td>
</tr>
<tr>
<td>• Edema</td>
<td>• Asymmetry and distortion</td>
</tr>
<tr>
<td>• Swelling</td>
<td>• Infections</td>
</tr>
<tr>
<td>• Hematomas and ecchymoses</td>
<td>• Necrosis: textural changes, physical consistency changes, and sensorial changes</td>
</tr>
<tr>
<td>• Pain</td>
<td>• “Rosacea-like” (^23) reaction: erythema, telangiectasias, and alteration of skin relief and consistency</td>
</tr>
<tr>
<td>Dyschromia</td>
<td>• Migration</td>
</tr>
<tr>
<td>Under or overcorrection</td>
<td>• Systemic diseases or complaints</td>
</tr>
<tr>
<td></td>
<td>• Lymph vessel blockage and embolism and their consequences (blindness, and so on)</td>
</tr>
<tr>
<td></td>
<td>• Bad aesthetic results</td>
</tr>
<tr>
<td></td>
<td>Filler or patient-related</td>
</tr>
<tr>
<td></td>
<td>• Allergies</td>
</tr>
<tr>
<td></td>
<td>• Recurrent edema with or without erythema/idiomsyncrasy</td>
</tr>
<tr>
<td></td>
<td>• Granuloma formation</td>
</tr>
<tr>
<td></td>
<td>• Other local reactions (infections, lipoatrophy, and so on)</td>
</tr>
</tbody>
</table>

Fig. 1 Raised lesions in the glabellar area of a patient who received previous injections of silicone.

Fig. 2 Perioral nodules due to previous silicone injections.
kava kava, celery root, fish oils) for 7 to 10 days before the procedure.\textsuperscript{10}

Some individuals may develop hypersensitivity reactions, which represent an exaggerated immune response to a foreign substance. Such anaphylactic type IV reactions generally occur within minutes of exposure to a challenging antigen owing to the release of histamine, which causes vascular permeability, edema, erythema, pain, and itching.\textsuperscript{12} Most of these reactions do not need any treatment. If the reaction persists, it can be treated with topical corticosteroid cream or intradermal corticosteroid injections.\textsuperscript{13} Minor complications such as erythema, redness, edema, swelling, pain, hematomas, and ecchymoses are self-limiting and deserve no additional medical treatment.

**Major Complications**

The main major complications are usually complications occurring late after LIS augmentation.

**Rosacea-Like Reaction**

“Rosacea-like”\textsuperscript{14} reactions can be observed with permanent fillers and is characterized by erythema, telangiectasias, and alteration of skin surface and consistency. It seems to be caused by excessive volume of permanent fillers and to be more frequent with methacrylate than silicones. Intense pulsed light or dye laser can be useful for these cases.

**Fibroplasia**

Although unusual with the microdroplet technique, it can occur due to overfrequent and excessive injections of large volumes of silicone. They can also be caused by superficial injections and silicone injections in areas of great mobility, such as the lips.\textsuperscript{15} Intralesional injections of low doses (0.5–5 mg) of diluted triamcinolone can be useful.

**Granulomas**

Several granulomatous reactions have been reported after using medical and nonmedical-grade silicone.\textsuperscript{16–18} Granuloma usually present late after injections, with tenderness, swelling, and at times suppuration.\textsuperscript{19} Granulomata should be excised and must be confirmed by histological examination: silicone granulomata show intracellular and extracellular nonbirefringent vacuoles (\textsuperscript{\textdegree}Fig. 3\textsuperscript{)}.\textsuperscript{18} Large-volume injection in one location, protein impurities, or irregularities of the surface may cause these granulomata.\textsuperscript{20} Two types of granulomata may appear after silicone injections: inflammatory and noninflammatory granulomata.\textsuperscript{2} Foreign body cells are present in both types, but the latter does not show acute inflammation.\textsuperscript{2} Granuloma size varies depending upon the volume injected.\textsuperscript{4,11,21}

According to Lloret et al, the correct management of granulomata consists of a physical examination, laboratory analysis (targeted to rule out an associated autoimmune disease), skin biopsy, and its microbiological culture. Radiographic studies can be performed to exclude soft tissue and bone inflammation. Ultrasonography and Doppler assure the correct position of the injected filler as well as vessel patency. Such granulomata can be treated with intralesional corticosteroids, preferably triamcinolone, and/or oral antibiotic therapy.\textsuperscript{10,11,22}

Other treatments that have been reported include allopurinol, surgical excision, isotretinoin, and other immunomodulating agents (oral, intramuscular, intravenous imiquimod).\textsuperscript{18,23,24} It is known that other fillers may also cause granulomas and can be treated similarly.

**Infections**

If the patient suffers from persistent herpes simplex infection in the areas injected by any filler, the infection can recur. It can be prevented by administration of antiviral medications starting at least 2 days postinjection and injections are contraindicated in active infection.\textsuperscript{25}

Inoculation of bacteria into the skin can occur during filler injection and due to impure material. Infection can also occur late, after a 2-week period of the implant placement. Early postprocedural infection may be treated with antibiotics and drainage. Complete resolution of all the cases is not possible, since biofilm formation may occur there. Biofilm is characterized as a living colony adherent to a foreign implant. Itself-encapsulates with a complex extracellular matrix consisting of polysaccharides.\textsuperscript{6,18,25} The risk of biofilm formation occurs during the procedure or after injections in the region of the implant, as well as during dental procedures and facial trauma. When it happens, the patient usually presents with recurrence of infection and chronicity. The treatment with antibiotics and drainage may suppress an active infection, but sometimes the implant should be surgically removed for complete resolution.\textsuperscript{25}

**Displacement or Migration**

Displacement or migration may occur with any injectable material. The migration of reabsorbable injectable material determines their temporary location in undesired sites, and
the migration of permanent injectable material localizes the material in undesired sites persistently. The possibility of migration is greater the lower the material viscosity and microparticle size, and the greater the volume of liquid injected. Migration was not observed in cases in which large volumes were implanted in serial injections, however, it can occur due to the action of gravity. According to biophysical knowledge, the action of two forces are necessary for migration to take place—the force of gravity and the propulsive force of the musculature, as well as the susceptibility of the material to the action of these forces. Additionally, being inert LIS is lighter than water, which is lighter than human tissue, thus its migration is impeded when implanted in microdroplets. The possibility of migration of LIS is also questioned because it has never been found in the cephalic segment resulting from injections in the caudal segments. In spite of being a process feared with the use of LIS, migration only occurs in special situations, as the consequence of bad technique or large volumes implanted in a single session.

Vascular Occlusion
Vascular occlusion can occur because of several reasons mostly related to the injection technique. Arterial occlusion becomes apparent early with severe pain and blanching. It is caused by direct arterial embolization of filler material. Prompt recognition and intervention is necessary. The area should be massaged and warm compresses applied, nitroglycerine paste can be also considered. Venous obstruction presents with livid discoloration and prolonged pain. It occurs later and when larger volumes are injected into a small area. The initial treatment is the same, in some cases antibiotics are necessary. The patient should be followed up closely and frequently. Conservative debridement should be performed in specific cases.

Conclusion
Transitory fillers seem to be safer than permanent fillers, such as LIS, and should be preferred by physicians. Proper technique and materials, injected by experienced physicians avoiding risky areas, and an optimal aesthetic treatment plan are crucial to prevent complications. Even being useless for the majority of dermatologists and aesthetic surgeons in the last decade, potential complications caused by LIS injections should be recognized, since complications can appear years after the treatment. Early medical care and treatment, including psychological support for these patients, can minimize the consequences for patients and physicians.

References
Prevention and Treatment of Complications after Polymethylmethacrylate-Microspheres Injections

Julia Vent, MD, PhD1 Gottfried Lemperle, MD, PhD2,3

1 Department of Otorhinolaryngology, Head and Neck Surgery, University of Heidelberg, Medical Center at Mannheim, Mannheim, Germany
2 Private Practice, Frankfurt am Main, Frankfurt, Germany
3 Clinical Professor, University of California-San Diego, San Diego, CA

Address for correspondence Julia Vent, MD, PhD, Department of Otorhinolaryngology, Head and Neck Surgery, University of Heidelberg, Medical Center at Mannheim, Theodor-Kutzer-Ufer 1-3, D-68167 Mannheim, Germany (e-mail: dr.julia.vent@gmail.com).


Abstract

Keywords
► Artecoll
► Artefill
► Metacrill
► PMMA
► granuloma
► adverse event
► complication management

The present article focuses on the peculiarities of polymethylmethacrylate as facial filler highlighting the injection technique, known adverse effects, and all options for complication management. Supplemented by a historical overview and case series, the authors share their experience with this widespread and in the last decade heavily criticized injectable filler substance.

There are various minimally invasive methods and injectable materials available for tissue augmentation to reduce the signs of an aging face, such as wrinkles and sagging, as well as concavities and fat hypoplasia.

Microspheres from acrylic substances as permanent injectable fillers have been developed in the late 1980s. When bovine collagen injections entered the market in 1981, the manufacturer promised a clinical effectiveness of up to 2 years (derived from collagen bulk injections on rats’ foreheads). The clinical experience, however, showed soon that the effect of fibrous and even cross-linked collagen injections in the human face lasted 3 to 6 months only. Therefore, research oriented toward substances which could prolong the effect of collagen injections—and discovered bone cement, consisting of microspheres of nonabsorbable polymethylmethacrylate (PMMA), to be the best biocompatible addition to collagen. At that time, microspheres a size of 30 to 40 µm in diameter were found to be ideal, being small enough to pass through small cannulas or needles but big enough to escape phagocytosis. The first mixture contained 20% PMMA and 80% bovine collagen, and was called Arteplast (Araucária Pr, Brazil). After analyzing the first granulomas in 1994, a high amount of small microspheres measuring less than 20 µm, which were prone to phagocytosis, were associated with foreign body reactions. Changing from dry sieving to wet sieving eliminated a high amount of these small particles, which had previously been attached to the bigger particles by static electricity during the dry sieving process. Further cleaning by washing with foam-forming tensides led to the two almost 100% clean products Artefill (Suneva Medical, Inc., San Diego, CA) and Artecoll (Hafod BioScience B.V., Nijmegen, the Netherlands) since 2006. Subsequently, the rate of granulomas decreased dramatically.

Artefill, manufactured by Suneva Medical, is an improved version of Artecoll and was approved by the Federal Drug Administration (FDA) in 2006 and is to date the only FDA-approved PMMA-filler in the United States. It has been injected in more than 120,000 patients in the United States and South Korea, as well as in Canada, under the brand name Bellafill. Artecoll, manufactured by Hafod BioScience B.V., has been approved in the European Union since 1994. It was sold in Canada under the brand name BellaFill.
Artesense. In China, Artecoll was Chinese State Food and Drug Administration (SFDA)-approved in 2004 and used worldwide in more than 500,000 patients. For safety reasons, the manufacturer recommended the epiperiosteal injection of Artecoll for facial volume augmentation, only. Marketing of Artecoll has been discontinued worldwide by the Chinese owner in 2008.

A third series of PMMA-injectables has been used in Brazil since 1998 under the brand names Metacrill (Nutricel Laboratorios, Rio de Janeiro, Brazil), Allianza, Brascher, New-Plastic, and Biossimetric by Linnea Safe (Lebon Laboratorios, Porto Alegre, Brazil). They all used crude PMMA-microspheres of all sizes (1–80 µm diameter) suspended in different cellulose gels, which are absorbed within a few days. Because of the high amount of small particles, granuloma rates were high in Brazil.

At present (2014), only Metacrill and Linnea Safe have approval of the Brazilian Health Ministry because both manufacturers could demonstrate significant cleaning of the microspheres in their products.

**Correct Injection Technique**

Choosing the correct instruments for injecting is crucial, blunt cannulas instead of sharp needles are preferred for strictly subdermal (Fig. 1A, B) and epiperiosteal injections. These blunt cannulas are less traumatic and cause less bruising by lateralizing subdermal vessels and remain automatically in the “right plane” by not intruding the dermis or the fascia.

The thickness of the facial dermis varies from 0.2 mm in the eye lids to 1.0 mm in the glabellar region, and is diminished to about one quarter of this in a wrinkle. The outer diameter of a 26-G needle is 0.45 mm (Fig. 1A). Therefore, all PMMA-injectables should be placed in the dermal–subdermal junction, except for acne scars which are augmented superficially. Intramuscular injection of PMMA filler is absolutely contraindicated, because the muscle dislocates any implant to unwanted sites and forms lumps. If intradermal blanching is seen during superficial injection of PMMA substances, the needle has to be withdrawn, the PMMA dispersed by firm massaging, and the needle inserted one needle diameter deeper. Later, little granules can occur (Fig. 2), which can easily be shaved with a scalpel or by dermabrasion.

Concerning posttreatment care, there is no reason to prevent the “physiological” swelling after injection, which allows macrophages and fibroblasts to invade the implant and encapsulate the particles or microspheres. Cold gel compresses may be comforting; however, there is no evidence that they prevent swelling or bruising. Reducing facial
muscle movement during the first days may prevent certain dislocation and clumping.

Beneath a wrinkle, Artefill, Artecoll, or the Brazilian PMMA-products have to be injected by moving the needle or cannula under constant pressure back and forth, thereby avoiding penetrating a subdermal vessel. Viewing the shape of the needle or cannula through the skin is evidence of being in the right plane of the dermal–subdermal junction (►Fig. 1A, B). It is preferable if the patient agrees to two or three sessions in a monthly sequence and not to inject the necessary volume during the first consultation.

Augmenting acne and traumatic scars is the only indication for superficial injection of PMMA products. Thereby, one has to see the gray of the needle in the skin, and blanching of the scar should occur. If blanching lasts for more than a few minutes, manual distribution of the injectable by massage is required.

In case of dark shadowed eyelids, the orbital rim has to be augmented strictly epiperiosteally by scratching the needle tip on the bony orbital rim. Care has to be taken to avoid injecting into the orbicularis muscle because of subsequent nodule formation (►Fig. 3).

Most side effects after lip augmentation occur in form of palpable or even visible nodules. Thus, while attempting to increase the volume of the vermillion, one must avoid implanting submucosal strands of any kind of filler, because muscle movement may compress strands into lumps (►Fig. 4). Instead, one should inject 30 to 50 submucosal droplets of a maximum of 0.01 mL along the dry-wet border (►Fig. 5A, B).

The horizontal filling of the vermillion border or "white roll" is a safe method. This restores the pouting appearance and eliminates the adjacent radial lip lines. An ideal anesthesia for the lips (faster and of shorter duration than an infraorbital block) is the injection of the local anesthetic into the maxillary labiogingival fold.

Complications after Injecting Polymethylmethacrylate Fillers

A series of publications on the advantages and disadvantages of PMMA fillers has been published recently,8–13 and their possible complications have been mentioned in detail,18–32 and reported to the FDA. Most of the published and presented granulomas have been caused by the impure Brazilian PMMA and Artecoll injected before 2006.33

Before treatment with PMMA, patients have to be informed about all known possible side effects, ranging from early and transient to late and persisting complications.

In patients prone to multiple allergies, a possible allergic reaction to bovine collagen has to be assessed before treatment. This affects an estimated 0.01% of patients injected with ArteFill or Artecoll.4 Skin testing on an invisible site such as the triceps area, will show an acute antibody reaction to the bovine collagen as a hot, red, swollen, coin-sized spot, often developing within 30 minutes. Overlooking an allergic reaction, the swelling, redness, and heat may start overnight and last for 3 to 7 days if not treated immediately with systemic steroids.

The list of complications also comprises adverse effects such as asymmetry after implantation and disappearance due to too deep injection or early facial muscle movement. Lumps in the lips or oral commissure can occur when the filler has been implanted into the orbicularis muscle and moved by the lip muscles during the 1st week after injection, when the
implant is still a paste.\textsuperscript{34} They may be prevented by the microdroplet injection technique (\textsuperscript{\textasteriskcentered}Fig. 5A, B).

Since PMMA-lumps show comparably little tissue ingrowth, steroids are not effective, so they have to be excised. In general, lumps appear within the first 4 weeks after injection; mostly, they occur solitary, well confined, located in the lips, and do not grow. True granulomas (\textsuperscript{\textasteriskcentered}Fig. 6A, B) appear late (mostly 6–24 months after injection), at all injected sites approximately at the same time. They grow rather fast and react well to intralesional steroid injections (\textsuperscript{\textasteriskcentered}Table 1). The incidence rate ranges between 0.01 and 0.1\%.\textsuperscript{33} The reason for the sudden onset of granulomas even after a long time may be the memory activation of macrophages, which are suddenly stimulated by a trigger such as systemic infection.\textsuperscript{33} Subdermal filler injections are at a particular risk of developing granuloma formations (\textsuperscript{\textasteriskcentered}Fig. 7) compared to epiperiosteal injections, which caused no granulomas so far.

Blanching can occur directly after implantation of any filler material when it is injected too superficially, except for scars, where blanching is required for correct implantation, and will disappear within 5 to 10 minutes. Blanching should be eliminated in any other case by firm smoothing motions applying pressure with a fingernail to force the material downward and sideways.

For grooves, ridges, or bulges (\textsuperscript{\textasteriskcentered}Fig. 2) that occur in spite of these precautionary actions, dermabrasion or surgical shaving were found to be the best treatment options, as the superficial wound will heal without scarring. If too superficial injection results in hypertrophic scarring (\textsuperscript{\textasteriskcentered}Fig. 2), intralesional triamcinolone injection will reduce the reaction and level the scar.

The serious complication of skin necrosis has been described for PMMA products from Brazil as well as for all other fillers,\textsuperscript{18,20,28} which have been implanted too deep subdermally through a resting needle, when the injection inadvertently blocked a subdermal artery. This disaster can be prevented by staying within the dermal–subdermal junction, where the vessels are smaller than the diameter of a needle, and by moving the needle constantly back and forth during injection.

Even blindness may occur after injecting PMMA. This has been described for all kinds of injectables, from autologous fat, anesthetics in the nose and periorbital area, to collagen and PMMA injections when injected into the glabella region.\textsuperscript{35} This extremely rare complication is due to a connection between the supratrochlear artery and the ophthalmic artery.

Ultrasonography and Doppler can assure the correct position of the injected material and vascular permeation of the tissue.\textsuperscript{36}

In the posttreatment period, the potential risk for infections has to be kept in mind. Every third person suffers from persistent labial herpes simplex infections. In these patients, the virus can be reactivated by implantation of any filler. Patients with a history of prior infections should be pretreated with valacyclovir (e.g., Valtrex [GlaxoSmithKline, Research Triangle Park, NC]) or acyclovir (e.g., Zovirax...
The best treatment at an early stage of reactivation is immediate treatment with acyclovir ointment, and at a later stage puncturing of the blisters. Infections of the injected sites such as bacterial superinfection should be avoided by thorough and sterile handling of the injectable, disinfecting the skin surface akin to presurgical preparations. If nonetheless infections do occur, disinfectant solutions and antibiotic ointments or even oral antibiotics should be applied.

**Treatment of Polymethylmethacrylate Granulomas**

**Granulomas**

Sclerosing foreign body granulomas after PMMA injectables are a serious and time-consuming complication. Since true foreign body granulomas are an overreaction similar to hypertrophic scars or keloids, the treatment of choice is immediate intralesional steroid injection with a high dose, not systemic steroid therapy.

Initially, a 1:1 mixture of lidocaine and triamcinolone 40 or 80 mg (Kenalog [Bristol-Myers Squibb Co., Princeton, NJ] or Volon-A [Dermapharm AG, Gruenwald, Germany]), prednisolone 40 or 80 mg (Depo-Medrol [Pharmacia & Upjohn Co., New York, NY]), or betamethasone 5 to 10 mg (Diprosone [MSD Merck & Co., Inc., Whitehouse Station, NJ]), can be injected safely through a 1-mL syringe with Luer taper or lock and a 30-G needle. It must be injected strictly into the granuloma, firmly held between two pinching fingers while guiding the needle tip back and forth under pressure. A strong resistance to the needle should be felt while “pumping up” the granulomas. As corticosteroids injected into the surrounding tissue may cause skin atrophy and necrosis, one should stop injecting as soon as the resistance of the nodule lessens, and restart from a different angle. Because of their high cellular content, granulomas are easier to inject than...
Table 2 The intralesional treatment of granulomas

<table>
<thead>
<tr>
<th>Intralesional treatments of granulomas</th>
<th>Concentration/dosage and application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triamcinolone</td>
<td>20–40 mg</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>5–7 mg</td>
</tr>
<tr>
<td>Methyl-prednisolone</td>
<td>20–40 mg undiluted</td>
</tr>
<tr>
<td>1/3 Betamethasone + 1/3 5-FU + 1/3 lidocaine (1%)</td>
<td>(3.5 mg) + (1.6 mL) + (1.0 mL)</td>
</tr>
<tr>
<td>Triamcinolone (10 mg/mL) + 5-FU (50 mg/mL)</td>
<td>(10 mg/mL) + (50 mg/mL)</td>
</tr>
</tbody>
</table>

Scary nodules and react faster, generally within 3 to 4 weeks. If there is no or little improvement after 3 to 4 weeks, the dose should be doubled in a second session, and eventually tripled in a third session.

In one Chinese patient with many granulomas after 114 syringes of Artecoll in her face, first 160 mg, then 240 mg, and finally 400 mg triamcinolone had to be injected to definitively resolve the granulomas. Some patients react very slowly to steroid injections: in that case, another steroid (see above) should be tried. It is suggested that betamethasone and prednisolone cause less skin atrophy than triamcinolone. Should skin atrophy occur, temporary filling with collagen or hyaluronic acid will level the indentation, until natural recovery occurs within 3 to 12 months. The patient should be informed and aware of this side effect after high doses.

Because of this danger of skin atrophy independent of the amount injected, there is a reluctance to use local corticosteroids on the part of many physicians. However, granulomas need high doses and will not dissolve under 10 mg triamcinolone.

Primary surgical excision is never indicated in granulomas, since the cause is a systemic cellular overreaction. Furthermore, surgery of granulomas will be incomplete in most cases because of their fingerlike invasiveness into the subcutis and nonconfined borders with the surrounding tissue.

In a series of an unselected sequential group of nine patients with granulomas under conservative management, all granulomas resolved within 2 years. Nevertheless, according to clinical experience, there are a number of patients resistant to steroid injections, requiring other treatment options such as bleomycin, minocycline, isotretinoin, allopurinol, azathioprine, imiquimod, or tacrolimus/FK506 cream.

The livid discoloration of some superficial sclerosing granulomas can be treated effectively by “flashing” with intense pulsed light in the same light wavelength range as targeting blood vessels. Four to five sessions not only block the neovascularization, but appear to soften and decrease the volume of the underlying granuloma, probably by reducing its blood supply from above.

**Skin Necrosis**

When the facial artery or its branches towards nose and lips have been blocked accidentally by an injectable filler material, the patient feels sudden pain after a few minutes and a localized skin area blanches and becomes pale or livid within hours. Case reports, for example, from Brazil have shown necrosis of half an upper or lower lip and of half a nose tip. Theoretically, the best immediate treatment is trying to push the PMMA bolus backward from the blocked artery into the facial artery with the fingernail. If this is performed extensively, vigorous massaging of the whole area should follow to increase blood flow and to open small arterial bypasses to this area. An intravenous infusion with dextran 40 or heparin may add to the blood flow around the blocked area. As soon as demarcation of the necrotic skin is obvious, the dead skin shall be removed and antibiotic ointment applied. Some superficial necrotic areas healed surprisingly well, others needed reconstruction with local skin grafts and mucosal flaps or even a forehead flap/Indian flap.

**Conclusion**

Most adverse events occurring after the injection of PMMA fillers can be prevented by proper injection technique. Artecoll and Artefill are less forgiving than hyaluronic acids and require more knowledge and experience, and a refined injection technique. The treatment of complications should be aggressive and initiated immediately after occurrence, either with corticosteroid injections or surgery. It is of utmost importance to know the clinical and histological difference between nodules and granulomas, because corticosteroids are effective in cellular proliferations but not in nodules of clumped particles or microspheres.

Nodules appear solely and early, for example, most often within the first few weeks after injection when the swelling is gone. They are hard, not growing, and not disappearing on their own. Nodules react seldomly to cortisone injections and should eventually be surgically removed.

Granulomas occur late, after 6 months to 6 years at all injected sites simultaneously. They mainly consist of macrophage invasion and fibroblast multiplication with little effect on the filler substance. The goal in the treatment of granulomas is to stop the invasion and proliferation of cells and the increased secretion of interstitial substances without leaving a scar. Triamcinolone and other steroids decrease both cellular proliferation and collagen production by dermal fibroblasts.

Foreign body granulomas after Artecoll injections have become a rare appearance since 2006, when a final purification of the microspheres in Artecoll was effected. Their cause is still unclear, but systemic infections, trauma, or surgery approximately 3 months before their onset have been suggested to stimulate the memory of macrophages, which suddenly attack the so far tolerated foreign, injected material.
Disclosure
The authors have no financial interest in any of the mentioned products.

References
Injection augmentation with alloplastic materials into the skin for cosmetic purposes has been known for centuries. Unregistered substances can cause severe adverse effects; especially oils (and their impure compounds) are known for producing subcutaneous inflammation. The use of substances to correct anatomical or surgical defects as well as body contours for reconstruction or cosmetic aims is old and began in 1899, when Robert Gersuny, an Austrian surgeon, injected a mineral oil (Vaseline) to correct the absence of a testicle in a patient who was castrated for tuberculous epididymitis.1–3 The immediate success of the operation encouraged him to use vaseline as a filler for soft tissue defects. He was also the first to use mineral oil for breast augmentation.

Adverse effects from oil injections were reported as early as 1906, when Heidingsfeld described disfiguring subcutaneous nodules in two patients who had received paraffin injections for facial wrinkles.4 Smetana and Bernhard coined the term “sclerosing lipogranuloma” in 1950 and it has been used since then as the most accurate description of the lesion caused by the injection of exogenous materials such as mineral or vegetable oils, specifically those containing short-chain saturated hydrocarbons.5

In this article, six cases presenting to the Department of Dermatology of the University of Sofia, Bulgaria, are described, after injection of oily vitamin preparations.

Case 1

In July 2011, a 26-year-old white female presented to the Department of Dermatology, University of Sofia, Bulgaria, after vitamin E injection for lip augmentation. Vitamin E gel had been extracted from yellow gel capsules. The procedure was performed in a cosmetic center by an esthetician without medical supervision. A few hours later, the patient developed...
painful edema in the injected perioral area, discharged yellow viscous material with an odor of the injected drug, and had difficulty opening her mouth.

Physical examination revealed a firm induration of the lips and perioral skin, tenderness, erythema, and two firm dermal nodules, one at the right nasolabial fold approximately 7 mm in diameter and a larger one, approximately 15 mm in diameter at the lower part of the right chin area near the midline (►Figs. 1A, B and 2A, B).

General physical examination and laboratory findings were unremarkable, and there were no systemic symptoms.

A 5-mm punch biopsy specimen was obtained. Histological analysis revealed numerous round-to-ovoid cavities of varying size in the dermis, resulting in a Swiss cheese-like appearance, consistent with a lipogranuloma. No tissue lipid analysis was performed (►Fig. 3A, B). We started treatment with systemic corticosteroids and a broad-spectrum antibiotic with good response. The edema resolved within 2 weeks.

**Case 2**

In April 2013, a 25-year-old white female presented to our department after vitamins A and E injection for lip augmentation.

Vitamins A and E had been extracted with syringes from Gericaps capsules and injected into her lips 2 months before admission to our hospital. The procedure had been repeated 5 days after the initial injection according to the patient’s demand, to get more noticeable lip augmentation. Three weeks after the second procedure, the patient developed painful edema and hardness in the injected area. The swelling extended within 1 week and involved the whole lips and surrounding perioral skin with difficulty opening the mouth.

Physical examination revealed a firm induration of the lips and perioral area, tenderness, erythema, and bilateral cervical lymphadenopathy (►Fig. 4A). Laboratory tests showed a white blood cell (WBC) count of 11,000/mm³, neutrophils 76.5%, and lymphocytes 14.5%.

A 5-mm punch biopsy was performed. Histological analysis revealed numerous round-to-ovoid cavities and vacuoles of variable sizes, invading the whole dermis, consistent with a lipogranuloma. No tissue lipid analysis was performed (►Fig. 5A–C).

Treatment with systemic corticosteroids and broad-spectrum antibiotic was instituted with good response (►Fig. 4B).

Three weeks after her discharge from the hospital and while she was on vacation to the seaside, two big tattoos were performed on her body by a professional tattoo artist according to the patient’s request. Also during this trip, she used a long-lasting lipstick borrowed from her friend, and spent many hours sunbathing at the beach. On the next day, she developed fever with gradual swelling of her lips (►Fig. 4C).

The patient was then readmitted to our hospital. Treatment with Solu-Medrol (methylprednisolone sodium succinate; Pfizer Manufacturing Belgium N.V./S.A., Puurs, Belgium)
40 mg/d, Tygacil (Tygceycline Wyeth Pharmaceuticals, UK; Wyeth Lederle S.r.l., Italy), 50 mg/100 mL NaCl 0.9%/d, 500 mg metronidazole (B. Braun Melsungen AG, Germany) twice a day, and Immunovenin (natural human immunoglobulin IgG 50 g/l infusion solution; Bul Bio-National Center of Infectious and Parasitic Diseases Ltd., Sofia, Bulgaria) 10 A/200 mL NaCl 0.9%/d was started. However, the patient continued to have fever with livid discoloration of the surrounding perioral skin area and discharge of yellow secretion from the lips (Fig. 4D). After consultation with an oro-maxillofacial surgeon, surgical intervention to debride the necrotic has to be performed.

**Case 3**

In April 2013, simultaneous to the admission of the second patient, a 21-year-old white female patient presented to our department after vitamins A and E injection for lip augmentation. Vitamins A and E had been extracted with syringes from Gericaps capsules and injected into her lips at the end of February 2013 by the same esthetician. Ten days after the procedure, the patient developed edema, induration, pruritus, and erythema of the lips and the perioral area. Physical examination revealed a firm induration of the lips and the perioral skin, two dermal nodules on the right and the left jaw line and a third one on the right side of the left orbicular area, together with bilateral cervical lymphadenopathy (Fig. 6).

The patient was febrile on the day of admission to the hospital. Laboratory findings showed WBC count 13,210/mm³, neutrophils 61.8%, lymphocyte 30.2%, and neutrophil count 8,200/mm³.

We started treatment with systemic corticosteroids and broad-spectrum antibiotic with good response. The symptoms resolved within 14 days.

**Case 4**

Three days after the admission of the third case, a 20-year-old white female patient presented to our department after vitamins A and E injection for lip augmentation. Vitamins A and E had been extracted with syringes from Gericaps capsules and injected into her lips at the end of January 2013 by the same esthetician of the previous two cases. After 1 month, she noticed four dermal nodules of different size involving both the upper and the lower lips and a fifth hard dermal nodule was palpated on the right side of the chin (Fig. 7A–D). Systemic corticosteroids and a broad-spectrum antibiotic were given with good response.

**Case 5**

In May 2013, a 38-year-old white female patient consulted our department after vitamins A and E injection for lip augmentation. The procedure had been done 2 months ago using vitamins A and E extracted from Gericaps capsules and injected into her lips by a physician.

One month after the procedure, the patient developed edema, induration, pruritus, and erythema of the lips and the perioral area. Physical examination revealed firm indurations of the lips and the perioral skin, erythema, and bilateral cervical lymphadenopathy (Fig. 8A, B). Laboratory tests showed a WBC count of 14,920/mm³, neutrophils 81.3%, and lymphocytes 13.1%.

A 5-mm punch biopsy specimen was obtained. Histological analysis revealed numerous dermal round-to-ovoid vacuoles of varying sizes consistent with a lipogranuloma. Marked thickening of the entire vessel walls with cavities containing the injected substance vitamins A and E and necrobiosis of the collagen were seen (Fig. 9A–C).

Again, treatment was started with systemic corticosteroid and broad-spectrum antibiotic with good response.

**Case 6**

On May 17, 2013, a 32-year-old white female patient presented to our department after vitamin E injection for lip
augmentation. The vitamin E had been extracted from yellow gel capsules; the procedure had been performed 1 month ago in a cosmetic center. Three weeks after the procedure, the patient developed edema and indurations in the injected area associated with pruritus and elevated local temperature (calor) of the lips and perioral area.

Physical examination revealed firm indurations of the lips and perioral skin, tenderness, erythema, and bilateral cervical lymphadenopathy (Fig. 10). General physical examination and laboratory findings were unremarkable. A patch test was performed to exclude a vitamin E allergy and the result was negative (Fig. 11).

We started the treatment with systemic and intralesional corticosteroids and a broad-spectrum antibiotic. The treatment was continued with intralesional triamcinolone acetonide and an oral nonsteroidal anti-inflammatory drug with good response.

**Discussion**

Various injectable substances have been used for lip augmentation over many years. Such substances are injected into the dermis or subcutaneous tissue to correct defects, for lipodystrophy, scars, and wrinkles or for tissue augmentation. All of them may cause adverse reactions either of early, intermediate, or late onset.

Sclerosing lipogranuloma is a skin condition characterized by a granulomatous and fibrotic reaction occurring in the subcutaneous fat from the injection of silicone or mineral oils. The body lacks the enzymes to metabolize interstitial exogenous oils and consequently a foreign body reaction develops.

Lipogranulomas arise from the injection of:

1. Mineral oils such as vaseline, paraffin oil, baby oil (mineral oil + fragrance), and automobile transmission fluid and oils
2. (Impure) silicone
3. Bees wax
4. Plant (vegetable) oils such as olive oil, walnut oil, sesame seed oil, almond oil and camphor oil
5. Lanolin
6. Cod liver oil
7. Autologous fat injection
8. Nandrolone decanoate (anabolic steroid)
9. Synthol, a mixture of 85% triglycerides, 7.5% benzyl alcohol, and 7.5% lidocaine
10. “Super Extenze,” a composition of mineral oil and vitamin E
11. Guaiacol, a natural phenolic product
12. Vitamin A in an oily vehicle
13. Injection of vitamin E
14. Polyvitamin-ADE complex, which contains liposoluble vitamins A, D, and/or E in an oily suspension

Vitamins A, D, E, and K are liposoluble vitamins. In many products, sterile peanut oil or soy oil is used. Vitamins A and/or E products injected for cosmetic aims contain some kind of oil, mineral, animal, or even vegetable. It can be concluded that the cosmetic and adverse effects of these vitamins are caused by the oily suspensions and not by the vitamins themselves, except for a possible hypervitaminosis caused by excessive administration.

Oil-soluble vitamins are less inert than other injected oils, such as paraffin, vaseline, and silicone. Perhaps, this is an
advantage compared with these oils, which can be absorbed and
resorbed by the body. However, it can also be a disadvantage, in case
the administered dose is not encapsulated by local biological
reactions leading to embolism or hypervitaminosis.  

In general, the clinical features of oil injection consist of the
following:

• Acute inflammatory phase (1–6 months after injection):
the intensity depends on the amount of oil injected, which
declines with time. This reaction may lead to skin
erythema, induration, edema and necrosis. Allergic
reactions may also occur, as well as vasculitis.

• Latent phase (during which the substance is tolerated):
this phase can take months, years, or decades.

• A final chronic and late phase (variable time interval):
when the macrophage response increases in an effort to
metabolize the foreign bodies through fragmentation,
which may lead to formation of sclerosing lipogranu-
loma. Fatty acids can combine with calcium, causing
calcification of the adipose tissue and hyaline sclerosis. The
time of onset of this chronic reaction, as well as the
intensity of damage is related to the amount of oil injected
and the tissue.

The most common adverse reactions are sclerodermoid
lesions, subcutaneous infiltrates, edema, and/or hyperpig-
mentation at the site of injection, deformation, and ulceration.
Infection and lymphadenopathy can also occur. The
granulomatous tissue may further undergo suppuration and
fistula formation with discharging sinuses. Adverse effects
are typically confined to the sites of injections and adjacent
skin areas, but there are also reports of involvement of lymph
nodes and lungs, presumably from the lymphatic or hema-
togenous spread. Hepatosplenomegaly and pulmonary
fibrosis may occur. Some patients also had lesions distal to the
site of application, other patients presented positive antinu-
clear antibodies. Acute renal failure, disseminated lipogranu-
lomas, and sudden death were reported. Long-term
follow-up is advised to determine the possibility of malignant
degeneration.

Histopathologically, sclerosing lipogranuloma formation is
seen. Granulomatous reactions caused by oily substances
develop in the affected tissues, demonstrating cavities of
different sizes located in the adipose tissue, from which an
oily matter may drain. Microscopically, this is called a “Swiss
cheese-like” image because it is possible to observe round
vacuoles and cavities that are not stained and represent the
space where the oily substance was located. This substance
disappears during histological processing. An inflammatory
infiltrate made up of lymphocytes, vacuolated macrophages,
and foreign body multinucleated giant cells can be observed.
next to the cavities. There are some histochemical techniques to stain oily substances in frozen sections. Sudan IV and oil red O stains may be used showing positivity through an orange coloration in the deposited material. If the foreign matter is paraffin or mineral oil, staining is recommended with the bromine-silver staining method, Baker phospholipid technique and osmic acid stains. The reason is that these oily materials are not fats and therefore negative to conventional stains. A study suggested that silicone can be double refractive when observed with polarized light, although this is not our experience.

The treatment of lipogranuloma is difficult. Immediate management is necessary to prevent disfiguring outcomes. Conservative treatment such as hot compression bandages can be applied as treatment in the early inflammatory phase. Adequate surgical removal of the oil from the tissues to prevent serious late sequelae should otherwise follow; however, it is associated with a high risk of scarring.

Glucocorticoids, both intralesional and systemic, are often used for their immunosuppressive and anti-inflammatory properties. Intralional steroid injections with insoluble triamcinolone crystal preparations are preferred. Allopurinol is ideal for treatment of larger and resistant-to-therapy lesions. Allopurinol probably exerts its therapeutic effect through antioxidant and anti-inflammatory properties, or by improving blood vessel function.

Colchicine acts as an anti-inflammatory agent by inhibition of granulocyte migration. The metabolic and mitotic activity of inflammatory cells is reduced, which in turn lessens the release of lactic acid and proinflammatory enzymes observed during phagocytosis. It also breaks the proinflammatory response cycle.

The use of allopurinol and colchicine should be the last option for the resistant cases, as should be the use of drainage or surgical extirpation due to the greater risk of leaving a scar. Other therapeutic alternatives include minocycline, cyclosporine, and 5-fluorouracil. Intralesional 808-nm diode laser light application dissolves the organic and synthetic components of the granulomas, facilitating subsequent evacuation. Recalcitrant granulomas occasionally require surgical excision.

The use of imiquimod (Aldara [imiquimod 5%, 3M]) to treat silicone-induced granulomas of the lip has been published.

Fig. 7 (A–D) Patient 4: five dermal nodules different in size involving both the upper and the lower lips and a fifth hard dermal nodule were palpated on the right side of the chin.

Fig. 8 (A, B) Patient 5: firm indurations of the lips and the perioral skin, erythema, and bilateral cervical lymph adenopathy.
Conclusion

The presented cases deal with complications caused by unregistered products injected as fillers by unprofessional physicians and beauticians. The illegal use resulted in serious adverse effects, which were difficult to treat. Facing these and other filler-induced complications, the need for a registered database on the web about the indications of fillers, filler types, as well as the possible side effects arises. This databank should also be easily accessible to the patients.

Conflict of Interest

The authors have no conflicts of interest, no specific financial interests and relationships and affiliations relevant to the subject of the article.
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Alginate (Novabel): A New Class of Injectable Filler

Pierre Andre, MD1  Isabelle Moulonguet, MD2

1 Rue de l’Université, Paris, France
2 Av Mathurin Moreau, Paris, France


Address for correspondence Pierre Andre, MD, 157, Rue de l’Université 75007 Paris, France (e-mail: pandre2@noos.fr).

Novabel was launched by Merz Aesthetics in January 2010 in seven European countries. It is a colorless and injectable, dermal filler composed of cross-linked alginate. It is supplied in a prefilled, 1 mL single-use syringe with two sterile 30 G 1/2 needles. Novabel is based on alginate, a natural and biocompatible polysaccharide, extracted from brown seaweed, which is a class of marine algae growing at the bottom of the ocean. The alginate undergoes intensive purification and stabilization to become a smooth, soft mass of microscopically three-dimensional particles of around 150 ± 50 μm, called “geleon.” The microspheres or geleons are saturated by the Ringer solution (less than 5% of the product). They are nontoxic, nonirritating, noncarcinogenic, and nonsensitizing. It was claimed that the human body does not react to the geleons (as if they did not exist) and that the immune system would therefore not be stimulated against them.

An 18-month clinical trial of 154 patients showed neither allergic reactions nor lump or granuloma formation. The consistency of the alginate was almost like water due to the uniform spherical shape of the geleons, thus requiring much lower injection force than with most other dermal fillers, particularly those of a gel-like consistency. This ease of injection was claimed to be due to a “shape memory” of the geleons which can change their shape while passing through a thin needle and regain their original shape when in place in the recipient tissue. This unique property was also thought to cause minimal swelling, bruising, and tissue damage. It could be shaped and molded for approximately 30 minutes after injection to give the desired effect. When the Ringer solution is absorbed by the body, it is no longer moldable and remains at the site of injection without migration. Hydrolysis slowly breaks the geleons down after a few months.

Use of the Alginate

Novabel was marketed as a nonpermanent product with a longer duration than hyaluronic acid.

Its viscosity is very low, which enables it to be injected through a very fine needle or flexible cannula.

According to the producer, this alginate is extremely pure and the endotoxin content would be less than 0.1 IU/mL. The product was said to be inert and would not require any skin testing, although the risk of granulomatous reactions had been reported.¹

Alginate is a nonpermanent product, which is degraded by nonenzymatic hydrolysis. The longevity of Novabel would be around 1 year. The first clinical trials performed before launching the product did not report any complications.

Keywords
► filler
► alginate
► filler complication
► granulomatous reaction
► Novabel

Abstract
A new class of biodegradable, injectable filler made of alginate, Novabel (Merz Aesthetics, Merz Pharma, UK), was launched in the European market in 2010. This product was supposed to be perfect to fill hollow eye rings and practitioners were immediately enthusiastic. Unfortunately, complications occurred as firm inflammatory nodules after a few months. Histological examinations revealed granulomatous reactions around spheroidal deposits. Treatment by triamcinolone injections was effective in some cases. Because of these complications, the company withdrew the alginate Novabel from the market. This is a didactic example of how a well-mean development with an insufficient test phase can turn into its opposite. Health authorities are exhorted to supervise not only drugs, but also injectables and other medical devices before they are launched, and during their application.

Issue Theme Filler Complications; Guest Editor, Eckart Haneke, MD, PhD

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When the product obtained the CE mark, many practitioners were enthusiastic because of the ease of injection and positioning.

The injections are performed into the deep dermis or deeper. Novabel was claimed to be the best product for the correction of hollow eye rings. In this area, the skin is thin and hyaluronic acid injections may have drawbacks: in case of a too superficial placement, a bluish aspect due to the Tyndall effect is undesired and in case of swelling due to the hydrophilicity of hyaluronic acid, a baggy aspect may occur. Both are aesthetically unsatisfactory.

As no swelling occurs after Novabel injection, the company emphasized the benefit over other fillers in infraorbital hollows. Advertising for treating patients around the eyes without risk resulted in infatuation of Novabel use.

**Observations**

Unfortunately, after a few months, many side effects were reported, particularly nodules under the eyes (Fig. 1 and 2). Despite the claim that the product is biodegradable, many customers complained of month- and year-long persistence of the nodules, which were particularly visible as the alginate was specially promoted for the treatment of hollow rings under the eye, where the skin is very thin.

The histological examination (Fig. 3 and 4) reveals a granulomatous reaction of variable size made up of macrophages and foreign-body giant cells around the geleon particles in the deep dermis or hypodermis. The alginate particles are spheroidal with occasional spicules and sometimes look like shrunken in clear vacuoles.

**Therapy**

No specific treatment is available up till now. However, without therapy, the complications last for a long time; many patients describe more than 2 years. Intralesoval injections of corticosteroid may help; however, there is a particular risk of atrophy of soft tissue and skin due to this therapy. In addition to steroids, the use of minocycline was advocated by the producer.

As the number of granulomatous reactions was too high, the company decided to withdraw Novabel from the market just after a little more than 5 months.

**Conclusion**

Side effects and adverse events are observed with any injectable fillers. In Europe, filling agents are considered as medical devices (as opposed to pharmaceutical medication)
and they may be launched on the market too early, without sufficiently long clinical studies.

For this reason, even if a product has obtained the CE mark, practitioners must be careful before using a new product or filling agent.

As adverse events to injectable fillers may appear months and even years after their injection, it is recommended not to use fillers before a closely monitored preclinical phase of at least 2 to 3 years. Injections of a new product should be followed by the practitioner for at least 1 to 2 years. Marketing arguments such as “biodegradable,” “natural,” “nonallergenic,” “nontoxic,” and many others should be received with caution and reviewed critically.

References
Diagnosis and Management of Filler Adverse Effects: An Algorithm

Gabriele Feller-Heppt, MD 1  Eckart Haneke, MD, PhD2  Markus V. Heppt, MD3

1 Skin and Face Clinic, Baden-Baden, Germany
2 Department of Dermatology, Inselspital, Universitätsspital Bern, Bern, Switzerland
3 Department of Dermatology and Allergy, Ludwig-Maximilian University, Munich, Germany


Abstract
Fillers are frequently used in beautifying procedures. Despite major advancements of the chemical and biological features of injected materials, filler-related adverse events may occur, and can substantially impact the clinical outcome. Filler granulomas become manifest as visible grains, nodules, or papules around the site of the primary injection. Early recognition and proper treatment of filler-related complications is important because effective treatment options are available. In this report, we provide a comprehensive overview of the differential diagnosis and diagnostics and develop an algorithm of successful therapy regimens.

Keywords
► injectable fillers
► side effects
► granuloma
► differential diagnosis
► treatment

After neurotoxins, fillers rank on the second place of beautifying procedures. It is an old wisdom that nothing with substantial efficacy does not—from time to time—cause adverse events as well. However, many side effects can be prevented obviating disappointment and ultimately litigation. Some fillers are more prone to cause adverse effects than others, but in principle, any injection, even of autologous material, introduces substances that are first recognized as foreign material. Sometimes, an objective measurement is necessary, which may require three-dimensional scanning.

The importance of an in-depth patient history cannot be overstated and it is central to know whether other procedures have been performed at the same time or previously. As most fillers are indeed predominantly injected into the facial area, an algorithm is given for this particular region.

In this article, we present an algorithm for differential diagnosis, diagnostics, and treatment of frequent side effects of injectable fillers.

Differential Diagnosis of Filler-Related Adverse Events
The most important visible filler side effects are swelling, bruising, necrosis, and ulceration.

Swellings are by far the most common and most diverse adverse effects. Important differential diagnoses are listed in Table 1. This table does not list congenital and other swellings that can easily be differentiated from filler-related complications, such as swellings in children or in the critically ill. The potential differential diagnoses responsible for facial swellings are numerous. It has to be kept in mind that some conditions, such as hereditary angioedema or Melkersson–Rosenthal syndrome can be provoked by the trauma of the injection procedure or by foreign bodies. Immunotherapy was also observed to induce granulomatous reactions to permanent fillers that had been well tolerated for many years. Fever is usually a sign of infection as in erysipelas and sometimes in abscesses, although "cold abscesses" do occur. Ultrasound did not substantially improve the differential diagnosis of solid swellings and cystic lesions such as abscesses. A skin rash may accompany the swelling. Overlying erythema may be a sign of a localized effect, whereas widespread skin lesions may point towards allergic reactions or a random association. An immediate onset is usually a sign of too much injected material, whereas appearance within a few hours or days may be due to allergic reaction. Granulomas and abscesses take many days to several weeks to develop clinically. In case the injected filler was a hyaluronan,
Table 1 Differential diagnostic evaluation of facial swellings that may be related to filler injections

<table>
<thead>
<tr>
<th>Swelling</th>
<th>Positive/negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of swellings and urticaaria</td>
<td></td>
</tr>
<tr>
<td>Atopy</td>
<td>Positive/negative</td>
</tr>
<tr>
<td>Medication</td>
<td>Yes/no²⁵,²⁶</td>
</tr>
<tr>
<td>Lymph node swelling</td>
<td>Yes/no</td>
</tr>
<tr>
<td>Previous injections</td>
<td>Yes/no</td>
</tr>
<tr>
<td>Diffuse</td>
<td></td>
</tr>
<tr>
<td>Onset</td>
<td>Acute/insidious</td>
</tr>
<tr>
<td>Event²⁸</td>
<td>Single/recurrent</td>
</tr>
<tr>
<td>Fever</td>
<td>Yes/no</td>
</tr>
<tr>
<td>Skin rash</td>
<td>Yes/no</td>
</tr>
<tr>
<td>Papules and pustules</td>
<td>Yes/no</td>
</tr>
<tr>
<td>Previous surgery</td>
<td>Yes/no</td>
</tr>
<tr>
<td>Localized</td>
<td></td>
</tr>
<tr>
<td>Previous injections³²</td>
<td></td>
</tr>
<tr>
<td>Hematoma</td>
<td></td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>Yes/no</td>
</tr>
<tr>
<td>Pain</td>
<td>Yes/no</td>
</tr>
<tr>
<td>Paresis</td>
<td>Yes/no</td>
</tr>
<tr>
<td>Orofacial granulomatosis</td>
<td>Yes/no</td>
</tr>
<tr>
<td>(Melkersson–Rosenthal syndrome,³⁶,³⁷ Crohn disease), oral mucosal lesions</td>
<td></td>
</tr>
<tr>
<td>Salivary gland infection</td>
<td>Yes/no</td>
</tr>
<tr>
<td>Abscess, infection³⁸</td>
<td></td>
</tr>
<tr>
<td>Arthropod assaults³⁹</td>
<td></td>
</tr>
<tr>
<td>Dental treatment</td>
<td>Yes/no</td>
</tr>
<tr>
<td>Tumor, lymphoma</td>
<td>Yes/no</td>
</tr>
</tbody>
</table>

Hyaluronidase injection will correct the overdose within a few hours.

Bruising (→Table 2) is a common sequel of any injection, and short-lived minor bruises are not listed as a major adverse side effect. However, as soft tissue augmentation is often performed in middle-aged and elderly persons, intake of anticoagulants may be expected and has to be asked for. For a long time, they have been judged as a contraindication for intramuscular injections. It is therefore reasonable to assume that they may increase the risk of major bruises and even large hematomas. These may, in turn, give rise to infection, necroses, and ulceration. Bruises usually disappear within a few weeks depending on their size and localization. Typical is a color change and the swelling may migrate downwards following gravity. Whether or not evacuation of the hematoma is necessary depends on the amount of blood.

Necroses (→Table 3) may be due to inadvertent intravascular injection or pressure on blood vessels by the injected material.³ Hyaluronic acid can be dissolved and degraded by hyaluronidase, which should always be readily available in any practice injecting hyaluronans. It should be injected immediately into the area where the filler has been placed. It has not yet convincingly been proven if the intravenous hyaluronidase infusion is feasible and efficient.⁵ It is advisable to use higher doses as these have a faster onset of action.⁵ Surgical debridement should be done very cautiously as some of the discolored skin may still recover, particularly areas with epitheliolysis only.

Ulceractions (→Table 4) usually develop from preexistent necroses and their treatment depends on the underlying condition. For instance, if the ulceration is due to hyaluronan, injection of hyaluronidase is the treatment of choice.

Papules and nodules may occur immediately and represent just overfilling or are a sign of an uneven injection technique. Frequently, however, papules, nodules, and infiltrates are characteristic signs of chronic inflammatory processes, most commonly of a granuloma or abscess. They represent late complications, some of which may be allergic whereas most are due to chronic histiocyte/macrophage stimulation. In contrast to acute inflammatory conditions, they are usually not warm or inflamed. The history of their development is critical for the correct diagnosis. We would like to emphasize that these complications may occur after injection of any filler, both temporary as well as permanent, and probably without major differences in frequency. However, most of the nodules due to temporary fillers have a limited period of persistence.

**Diagnostics**

Most patients seeking consultation for filler complication treatment received an external injection. Thus, taking a thorough and specific history is a central cue to the correct diagnosis.

Depending on the onset and the clinical appearance of filler side effects, several different diagnostic means are used. Whereas symptoms such as swelling, bruising or a certain sensation of pressure does not require therapy, a variety of local and systemic treatment options are available in case of moderate and severe complications. These include blood tests and microbiological examinations in case of suspected bacterial infection or if systemic reactions such as fever, headache, muscle pains, fatigue, and malaise are present.

Modern imaging methods and analyses improve the accuracy of differentiated topodiagnosis (→Fig. 1).⁶ B-mode ultrasound examinations have their special value in the assessment of nodular formations in terms of abscess and lymph node diagnostics and in the therapeutic follow-up. Together with modern nuclear medicine, including white blood cell scintigraphy, high-resolution computed tomography, and magnetic resonance imaging, it is possible to differentiate between infection, granuloma formation, and fibrosis these days.⁶–¹² Despite these advancements in accurate imaging, the ultimate identification of certain filler substances—if not evident from the patient’s history—requires histopathological investigation (→Fig. 2), or optionally characterization by chromatography, mass spectrometry, or capillary electrophoresis.¹⁰
Treatment Options

The selection of an appropriate treatment regimen in filler-induced adverse events depends on filler material, clinical onset of complications, the duration of granulomas, localization, and degree (Table 5). For instance, it makes a big difference whether a swelling and induration occurs one day after treatment with pure hyaluronic acid or a few months after polymethyl methacrylate injection.

Among the most serious adverse effects are prolonged blanching followed by painful vascular compromise, necrosis, or ulceration, blindness due to vascular injection in the glabella and granuloma tissue formation. Using blunt cannulas for injections instead of sharp needles markedly reduce the risk for intravascular injections and vascular compromises, avoidance of the use of more than one filler at the same time and the same injection site in general diminishes the complication rate. Unpleasing aesthetic results belong, strictly speaking, not to filler complications, but should be treated similarly. In the vast majority of cases, they are due to asymmetric augmentation or overfilling with hyaluronic acid. Because of its hygroscopic
chemical features, an apparently good result immediately after injection may change towards a mediocre outcome on the following day. Particularly, the periorbital area with loose connective tissue is prone to develop swelling and edema exposing visible overcorrection (►Fig. 3). Local injection with hyaluronidase (Hyalase [Riemser Pharma, Greifswald, Germany]), the antidote of hyaluronic acid, will effectively solve this problem.17–19 The solution for injection contains 75 U/0.5 mL NaCl added to 1.5 mL lidocaine, supplemented with 1% adrenaline. In general, 5 to 50 U of hyaluronidase are used per nodule. Response to injection can be expected within 24 to 72 hours, reinjection after 1 week is possible.

To quickly and most effectively treat severe early adverse effects such as vascular compromise physicians should be trained in early detection and medical handling. Agents such as nitro paste or hyaluronidase (►Fig. 4) and cool or warming pads should be ready to handle.

The treatment modalities of granulomas are different. They require great experience and proper selection of a treatment regimen out of many possibilities (►Table 6). Interdisciplinary planning and profound knowledge of the pharmacology of eligible agents are basic conditions for a successful outcome. The first-line therapy of granulomas is based on the intralesional injection of crystalline steroids, even despite the risk of skin atrophy. Topical immunomodulating agents and immune response modifiers such as imiquimod (Aldara, Zyclara), 0.1% tacrolimus ointment (Protopic), and pimecrolimus cream (Elidel) are best suited for initial therapy of superficial granulomatous inflammation (►Fig. 5).

In cases resistant to steroidal and immunomodulatory treatment, mostly side effects of permanent fillers, intralesional 5-fluorouracil (5-FU) injections can be considered15,19 (►Fig. 6). A possible solution for injection contains 0.8 mL 5-FU 250 mg/mL added by 0.1 mL triamcinolone 10 mg/mL and 0.1 mL of 1% scandicaine. In patients with permanent recalcitrant filler granuloma, this treatment may be combined with the oral administration of allopurinol.20 Initially 200 mg/d is given in the first 2 weeks, followed by an increase to 400 mg/d in week 3, and a further increase to 600 mg per day from week 4 as maintenance dose. This treatment extends several months, depending on the clinical course. It may be flanked by systemic corticosteroids in acute inflamed granulomas as well as and antibiotics if superinfection is suspected clinically.

Surgical excision of granuloma tissue formation is an option of last resort, if all other conservative treatment options fail. Dangerous filler migration, tumor growth, and increasing aesthetic compromise are some indications (►Fig. 7A). Due to the finger-like growth pattern of the diffusely distributed filler substances, the recurrence rate is high and complete removal cannot be achieved in most cases.
Beside all therapeutic efforts, proper patient selection may prevent from later calamities. Patients suffering from acute systemic infections or skin infections at injection sites, known allergies to injection materials or egg white, severe autoinflammatory disorders, and major cardiac dysfunction should not be treated, neither those reporting multiple intolerance reactions.\textsuperscript{21,22} If allergic reactions are suspected clinically, skin testing has to be considered.

Table 5 General treatment recommendations in filler side effects

<table>
<thead>
<tr>
<th>Clinical symptom</th>
<th>Therapeutic strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiological reactions such as swelling,</td>
<td>Cooling, nonsteroidal antiphlogistics</td>
</tr>
<tr>
<td>sensation of pressure</td>
<td></td>
</tr>
<tr>
<td>Overtreatment of hyaluronic acid (HA)</td>
<td>Hyaluronidase (Hyalase) = antidote of HA</td>
</tr>
<tr>
<td>Asymmetry</td>
<td>Touch-up filler injection, in case of HA localized hyaluronidase injection</td>
</tr>
<tr>
<td>Vascular compromise</td>
<td>Nitro paste, acetylsalicylic acid, heparin-infusion, warming, hyaluronidase after HA</td>
</tr>
<tr>
<td>Necrosis, ulcerations</td>
<td>Sterile, antiseptic wound treatment, surgical debridement</td>
</tr>
<tr>
<td>Hematoma</td>
<td>Heparin ointment</td>
</tr>
<tr>
<td>Discoloration</td>
<td>Blush discoloration due to vessel dilatation: intense pulsed light (IPL), laser</td>
</tr>
<tr>
<td>Nodules</td>
<td>Puncture to distinguish sterile from bacterial abscess</td>
</tr>
<tr>
<td></td>
<td>Sterile abscess: intralesional corticosteroids (cave atrophy), excision of superficial nodules resistant to topical therapy</td>
</tr>
<tr>
<td></td>
<td>Suppurative abscess: antibiotics, incision</td>
</tr>
<tr>
<td>Hypertrophic scar at injection site</td>
<td>Intrallesional steroid, dermabrasion</td>
</tr>
<tr>
<td>Granuloma</td>
<td>Anti-inflammatory and/or immunomodulatory therapy, surgical removal</td>
</tr>
<tr>
<td>All kinds of side effects</td>
<td>Compelling information on treatment, medicolegal aspects, and payment</td>
</tr>
<tr>
<td></td>
<td>Good psychological support</td>
</tr>
</tbody>
</table>

Fig. 4 Vascular compromise due to injection of hyaluronic acid with a sharp 27 G needle. After development of a painful blanching, the concerned area of facial artery and vein was injected by Hylase Dessau 150 U/mL NaCl and also superficially treated with the vasodilative nitro paste. Pain and swelling quickly decreased, but on day 1 after treatment (A) the patient presented with a dusky red discoloration, with significant relief on day 3 (B), day 7 (C), and day 14 (D). White area shown in (B) resulted from the removal of makeup.
in advance.\textsuperscript{23,24} To keep the risk of a filler side effect as low as possible patients are advised to refrain from extensive sun exposure, sauna, and substantial physical exertion.

Not to be forgotten in the context of filler complications are medicolegal aspects. Patients must be informed about all possible complications and informed consent must be obtained before injection. Also, they should be advised that all costs of treatment have to be covered at their own expense, since aesthetic procedures and their complications are non-insured medical events.

A good psychological support from the very beginning of the onset of a filler side effect is just as important as medical care. It is of paramount importance to provide the patient with all necessary information. This should be best done in a reassuring but concise way in an empathetic and professional atmosphere.

Whenever signs of psychological decompensation first appear the indication of immediate psychiatric treatment should be considered.

\textbf{Conclusion}

The use of injectable fillers in aesthetic medicine is safe if applied professionally according to the principles of good clinical practice. Before injection, patients should be comprehensively informed about the actual procedures.

\begin{table}
\centering
\caption{Table 6 Therapy options in filler-induced granulomas}
\begin{tabular}{|l|l|}
\hline
Entry & Description \hline
Hyaluronidase for treatment of hyaluronidase injection-induced granuloma & Solution for injection: 75 U/0.5 mL NaCl + 1.5 mL lidocaine supplemented with 1% adrenaline Use 5–50 U hyaluronidase per nodule Response to injection can be expected within 24–72 h, reinjection after 1 week possible \hline
Topical immunomodulating agents and immune response modifiers (imiquimod: Aldara, Zyclara; tacrolimus: 0.1% Protopic ointment; pimecrolimus: Elidel cream) for superficial granulomatous inflammation & Treatment twice daily for a minimum of 14 d Treatment duration up to several months in case of good response \hline
Intralesional triamcinolone (10 mg/mL) in bigger nodules caused by degradable or permanent fillers & Initially, 0.1 mL per granuloma in weekly intervals (up to 4 wk) In case of good response, injections should be performed monthly for 3–6 mo (cave of skin atrophy) \hline
Intralesional 5-fluorouracil (5-FU) injections for granuloma due to permanent fillers (Dermalive, and so on) (Protective eyewear during injection procedure) & Solution for injection: 0.8 mL 5-FU 250 mg/mL + 0.1 mL triamcinolone 10 mg/mL, supplemented with 0.1 mL scadicaine 1% At maximum 1–1.5 mL each session Therapy at weekly intervals initially, intervals can be expanded in the course of treatment Duration of treatment: months to years \hline
Oral allopurinol for permanent filler granuloma, where applicable combined with 5-FU injections & 200 mg/d in the first 2 wk, increase to 400 mg/d in wk 3, and further to 600 mg/d from wk 4 as maintenance dose Duration of treatment: months \hline
Systemic corticosteroids in acute inflamed granuloma, for example, after polyactic acid (Sculptra) & Prednisolone 20–80 mg/d, adjusted to body weight Duration and tapering: up to 4 wk depending on the clinical course \hline
Surgical excision as final treatment option & \hline
Oral antibiotics if superinfection is suspected clinically & Cefuroxime 500 mg twice a day \hline
\end{tabular}
\end{table}
Filler-related adverse events should be part of the informed consent, specifically, granulomas, papules, nodules, subcutaneous swelling, bruising, necrosis, and ulceration. If these side effects are recognized early prompt therapy should be initiated, based on the clinical symptoms and the injected materials. Proper handling can help to improve the clinical outcome and mitigate disappointment. Hyaluronic acid-products have found to be the safest fillers and the only ones with a real antidote.

Fig. 6 Successful treatment of a patient suffering from therapy-resistant granulomas after Dermalive injections (hydroxy-ethyl-methacrylate, ethyl-methacrylate, hyaluronic acid) into the nasolabial fold 7 years after injection. Clinical view before (A) and 6 months after therapy (B) with 5-fluorouracil (5-FU). Intralesional injections of 1 to 1.5 mL of 5-FU 250 mg/0.8 mL, supplemented with triamcinolonaacetin 0.1 mL and scandicaine 1% 0.1 mL, according to the treatment scheme of Table 6. Sonographic checks before (C), after 7 months (D), and 9 months (E) show significant reduction of granuloma formation. Biopsy taken before treatment shows foreign-body giant cells (arrows), macrophages, and lymphatic infiltration (F).
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Reconstruction of the medial canthal area and lacrimal apparatus following tumor resection presents multiple challenges. A part of this challenge lies in recreating the complex three-dimensional anatomy of the medial canthal area and in achieving a functional result that avoids chronic epiphora. Challenges associated with surgical reconstruction of the medial canthus alone include matching recipient-site skin color and texture, minimizing donor-site morbidity, and camouflaging the resultant scars. In addition, the importance of preserving the normal concavity of the medial canthal region and avoiding distortion of the surrounding eyelids, eyelashes, nasal dorsum, and glabellar regions should not be overlooked. Preventing exposure of the globe is also crucial from an aesthetic and functional standpoint as overexposure may result in infection or ocular injury.

Various techniques for reconstruction of medial canthal defects have been reported, including midline and paramedian forehead flaps (PMFFs), full thickness skin grafts, glabellar flaps, rotational flaps, bilobed flaps, transpositional flaps, z-plasties, and rhomboid flaps. However, most of these techniques struggle to overcome all of the challenges described above, and do not address the additional obstacle of reconstruction of the lacrimal outflow tract.

Epiphora after surgical resection in this region results from structural eyelid changes, alterations in tear flow toward the medial canthus, or failure of flow within the outflow tract. The outflow tract has traditionally been reconstructed with dacrocystorhinostomy and often requires the use of a Jones tube. Some authors have even advocated for a delay of up to 5 years before reconstructing the outflow tract due to concerns of facilitating tumor spread endonasally during dacrocystorhinostomy.

In this case series with retrospective review, we describe and illustrate a surgical technique using a PMFF and an AlloDerm (LifeCell Corporation, Township of Branchburg, NJ) as the conduit for reconstruction of the medial canthus and lacrimal outflow tract. We present a case series of three patients successfully reconstructed with the above technique and describe their presentation, treatment, and postoperative course. We provide a detailed description of the surgical technique and document the success of the technique in regard to patency and postprocedure function of the lacrimal conduit.
Methods

After approval by the institutional review board, we identified three patients that underwent medial canthal and lacrimal outflow tract reconstruction using a PMFF combined with an AlloDerm conduit graft after tumor excision. All patients had a minimum follow-up of 1 year. Patient records from our institutional electronic medical record database were accessed for review and data collection. Data points included age, gender, preoperative diagnosis, tumor size and location, involved structures, surgical procedure, postoperative diagnosis, duration of follow-up, functional results (including lacrimal duct patency), evidence of tumor control or recurrence, complications (including epiphora, infection, and graft viability), and before and after photographs of the tumors and involved areas.

Report of Cases

Case 1
A 64-year-old male patient was referred for basal cell carcinoma of the right medial canthus. The lesion was present for several years and recurred after undergoing cryotherapy during that time. The lesion measured 2 × 2.5 cm and extended to involve the ipsilateral medial canthal tendon and lacrimal sac (Fig. 1). Excision with frozen section control was performed (Fig. 2), and reconstruction using this technique was performed. The 6-month postoperative result is shown in Fig. 3. The patient’s last follow-up appointment was at 12 months after reconstruction. There was no evidence of tumor recurrence or epiphora.

Case 2
A 66-year-old male patient was referred for recurrent basal cell carcinoma of the right medial canthus. The recurrent lesion measured 1.5 cm and extended to involve the medial canthal tendons and lacrimal apparatus. Excision with frozen section control was performed, and reconstruction using this technique was performed. The patient’s last follow-up appointment was at 18 months after reconstruction. There was no evidence of tumor recurrence or epiphora.

Case 3
A 53-year-old male patient was referred for basal cell carcinoma of the left medial canthus. The lesion measured 5 × 3.5 cm and extended to involve the left upper and lower eyelids and the skin of the cheek. Excision with frozen section control was performed, and reconstruction using this technique was performed. The patient’s last follow-up appointment was at 13 months after reconstruction. There was no evidence of tumor recurrence or epiphora.

Surgical Technique

Initially, clearance of the tumor margins is achieved either via Mohs micrographic surgery or, as in the cases described here, intraoperative frozen section control. If there is bony involvement by the tumor, then reconstruction is delayed until permanent section with decalcification demonstrates...
complete and adequate tumor resection. If there is a question of whether a margin is clear or not, the surgeon may elect to postpone reconstruction and allow the defect to heal by second intention. This is followed by a period of observation to avoid covering tumor recurrence with a flap. The technique described here is intended for use in large defects that require sacrifice of the medial canthal tendon, lacrimal sac and canaliculi, and typically involve bone of the lacrimal crest and lamina papyracea.

Once the margins are demonstrated to be clear, the defect is measured and a piece of material such as Telfa (The Kendall Company, LTD; Basingstoke, Hampshire, UK) or a foil suture packet is used as a template to model the defect. Care is taken to contour the Telfa or foil into the defect to ensure adequate size. This template is then used in the design of the PMFF as has been described extensively elsewhere.5–7 The PMFF is thinned over most of the skin paddle corresponding to the defect, as the medial canthal and eyelid skin is typically much thinner than the forehead skin. The flap will commonly be shaped in a rounded “Y” fashion to extend onto the upper and lower lid as needed.

Attention is turned to reconstruction of the lacrimal outflow tract. If there is no preexisting defect into the nasal cavity through the lamina papyracea from the tumor ablation, a 1 to 2 cm defect is created at this time. The remaining conjunctiva in the area of the caruncle is mobilized and tunneled into this defect (Fig. 4) and secured with 5–0 chromic suture to the nasal mucosa, creating the posterior wall of the conduit (Fig. 5). A thin, graftable, AlloDerm graft is tunneled into the lamina papyracea defect and sutured to the nasal mucosa, previously tunneled conjunctiva, and then to the edges of the flap to create a tube of 1 to 1.5 cm diameter extending from the caruncle into the nasal cavity (Fig. 6). The PMFF is then inset to the edges of the defect including the eyelids and tarsal plate as indicated by the remaining eyelid structures (Figs. 7 and 8). If most of the eyelids remain, the canthal tendon can be reconstructed directly with a permanent suture such as 4–0 Mersilene (Ethicon, Somerville, NJ). In most cases, the remaining eyelid will be sutured directly to the “Y” of the PMFF with 4–0 PDS or similar suture.

If an interpolated PMFF is used, the pedicle portion of the flap is removed at 3 weeks, and the remainder of the flap is inset along the medial portion of the defect at that time. The flap can alternatively be designed as a single-stage flap, inserting the pedicle portion across the glabella and nasion at the initial procedure. Patients are seen at 1 week, 1 month, and then every 3 months afterward for tumor surveillance. At present, a positron emission tomography/computed tomography is obtained at 3 and 12 months to assess for recurrent disease.

**Results**

The above technique was performed in three patients between July 2010 and February 2012, and all patients were compliant with follow-up appointments ranging from 12 to 18 months postreconstruction. All patients were male, and their ages ranged from 53 to 67 years. The common diagnosis in each case was basal cell carcinoma of the medial canthus with involvement of the lacrimal apparatus, with or without additional involvement of other structures. The tumors...
ranged in size from 1.5 to 5 cm in greatest dimension. All patients were disease free without any signs of cancer recurrence at their most recent follow-up visit. There were no postoperative infections, and all grafts remained intact and viable for the duration of follow-up. The reconstructed lacrimal duct was also found to be patent and functional throughout the treatment course of each patient. Complications of case 1 included mild entropion and trichiasis, which resolved with outpatient correction. Complications of cases 2 and 3 included minimal epiphora that was reported only in the early follow-up period, and which resolved spontaneously without intervention during the course of follow-up.

Discussion

Defects of the medial canthal area present a difficult reconstructive challenge. When coupled with reconstruction of the lacrimal apparatus, this endeavor grows even more challenging as the reconstructive surgeon strives to achieve desirable functional and aesthetic outcomes. We have utilized the above technique with low complication rates and excellent functional and aesthetic results.

Other previously described techniques for repair of medial canthal defects include full-thickness skin grafts, glabellar flaps, rotational flaps, bilobed flaps, transpositional flaps, z-plasties, and rhomboid flaps. Depending on the exact defect size and location, all of these techniques are potentially useful, but no single technique is suitable for all defects in this region. Full-thickness skin grafts often struggle to match the recipient tissue color and texture, and are prone to partial or total graft failure. Additionally, the other local flaps described above may struggle to facilitate a completely tension-free wound closure. The amount of locally available tissue is limited in this region, and these local flaps often do not bring in as much tissue as a forehead flap. The importance of tension-free closure in this region cannot be overstated as even minimal tension can distort the eyelids, interrupt tear flow, and drastically impact the aesthetic result. Forehead flaps, especially the PMFF, are hardy, dependable choices for reconstruction of medial canthal defects. A reliable blood supply and pliability of the donor tissue enable thinning of the flap for better approximation, and the similarity of the donor-site tissue to the recipient-site tissues ensure its continued use in this setting.

In addition, we believe the use of the AlloDerm graft described in our technique is a good option for establishing a patent outflow tract into the nasal cavity to avoid epiphora, and is a simplified technique for reconstruction of the lacrimal apparatus through avoiding the use of a cannula or Jones tube to maintain patency of the nasolacrimal neopassage. Complications associated with lacrimal bypass tubes include extrusion, displacement or migration, obstruction, infection, poor cosmesis, and other ocular problems including ocular ulceration, scleral erosion, ocular discomfort, retrograde air blowing, diplopia, and dry eye secondary to overdrainage. Infection rates as high as 10% have also been reported. These synthetic tubes also require protection of the lateral aspect of the tube during sneezing or nose blowing and frequent care and cleaning. This AlloDerm graft does not require removal or any additional care. The material is sewn into place in several locations and is supported by the forehead flap and surrounding soft tissues, limiting its movement. Overtime, the graft material is integrated into the patient’s tissues, making it a permanent conduit. With this technique, we have not experienced any cases of infection, conduit migration, or long-term epiphora.
Limitations of this study and the described technique include the limited number of patients included in our series, and a lack of literature regarding the use of AlloDerm as a conduit for reconstruction of the lacrimal apparatus. Furthermore, although the PMFF was useful for these patients, it has been described elsewhere as being too bulky, inflexible, and containing an overabundance of glandular tissue to be the ideal flap for reconstruction of the medial canthal region.\(^{10,11}\) Additionally, flap failure and necrosis can occur secondary to inadvertently damaging the arterial supply, excessive thinning of the flap while attempting to achieve appropriate contour, vessel kinking, or venous outflow obstruction. For these reasons, we concede that there is a need for further investigation on a larger scale to verify this technique as a proven alternative for medial canthal reconstruction. Despite these criticisms, we believe that the technique presented here offers a promising role in the reconstruction of combined medial canthal and lacrimal apparatus defects.

**Conclusion**

Medial canthal defects present a reconstructive challenge, particularly when the defects also involve the lacrimal system. The use of a PMFF and an AlloDerm graft (as the conduit) is an efficient and effective technique for reconstructing these defects following tumor excision. This technique results in excellent functional and aesthetic outcomes with low morbidity and should be considered as a reconstruction option for these patients.

**References**

Nasal Lift—Nasal Valve Lift and Nasal Tip Lift—Preliminary Results of a New Technique Using Noninvasive Self-Retaining Unidirectional Nasal Suspension with Threads

Yves Saban, MD1  De Benito Javier, MD2  Michela Massa, MD3

1 Department of Otorhinolaryngology, Maxillofacial Surgery, French Facial Plastic Surgery Society, Nice, France
2 Department of Plastic and Reconstructive and Aesthetic Surgery, International Society Aesthetic and Plastic Surgery (ISAPS), Barcelona, Spain
3 Department of Plastic and Reconstructive Surgery, Genoa University, Genoa, Italy


Address for correspondence Michela Massa, MD, Department of Plastic and Reconstructive Surgery, Genoa University, IRCCS San Martino IST. L.go Rosanna Benzi 10, 16132 Genoa, Italy (e-mail: michelamassa01@gmail.com).

Abstract

In the context of nasal obstruction treatment, an alternative, no invasive technique is described. It consists in the suspension of the nasal valve or in the association of the suspension of the valve and rotation of the tip, through the placement of one or two absorbable threads, already known in aesthetic medicine. This technique allows to open the nasal valve and to correct the moderate closure of the nasolabial angle obtaining an immediate benefit of breathing. Functional improvement has been evaluated at regular intervals, that is, 1, 3, 6, and 12 months and then provided for every 6 months, through the use of a visual scale of 0/10 to 10/10. In our experience, the technique allows to obtain satisfactory results, avoiding more invasive techniques and postoperative recovery days.

Keywords

► nasal valve
► nasal lift
► absorbable threads
► airflow obstruction

“Among all freedoms, nasal freedom is one of the most precious!”

This phrase, commonly cited by Prof. Wayoff among our rhinology specialists, summarizes the importance of nasal respiration. Airway obstruction is a subjective sensation resulting from a complex interaction of the nasal structures with the environment depending on various factors, such as pathologies associated and patient perception level.1 The physician’s role is to identify the cause or causes of chronic nasal obstruction to be able to offer the patient the simplest and most effective therapeutic solution. This initial diagnostic approach is essential; it is based on the knowledge of local pathologies, their identification, and the recognition of their role in symptoms experienced by the patient. The conception of nasal obstruction as a mixture of several different sensations has been developed by recent experimental and clinical data.2 These results may explain the varying correlation between the objective measures and the subjective sensation of the airflow.3 The sensation of ventilatory airflow takes place at three anatomical levels of varying interrelation:

1. The nasal valve (►Fig. 1) is a converging–diverging adjuster whose outer wall collapses when the transmural pressure is less than the intranasal pressure (8 cm of water on an average).

This collapse occurs in approximately 13% of the normal population, but the lateral wall weakness may be the

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consequence of an alar displacement, a trauma or a surgical procedure that reduces the parietal resistance. The angle of the internal valve with the septum is 10 degrees.

2. The septum is the central wall whose anterior deformations are recognized as the most symptomatic, precisely facing or behind the nasal valve.

3. The inferior turbinates, especially in their anterior part, have a variable volume, which is an essential component of the obstruction.

The reduction of inferior turbinate volume causes a disorganization of the airflow and the emergence of resistance areas and turbulence due to pressure gradient variation and shear stress. The numerical simulations allow glimpsing the empty nose syndrome mechanism.

Oral respiration can become a temporary and sometimes permanent solution when the upper airflow is compromised or insufficient. Physiologically, oral respiration is required when high flow rates of oxygenation are necessary, notably during significant physical effort and particularly among sportsmen. Nasal respiration can also be compromised in many pathological situations. Respiratory allergies currently affect more than 20% of the world’s population and are classified by the World Health Organization in the top five of the world’s most widespread illnesses.

In adults, the causes of nasal obstruction are mostly mechanical and related to abnormalities of the nasal septum, turbinate hypertrophy, closure of the nasolabial angle, abnormality of the nasal valves. The etiological recognition is a crucial step toward the therapeutic decision.

Investigations in rhinology are summarized as morphological and functional explorations whose main problem is to establish the correspondence between the symptoms described by the patient and the abnormalities found during these examinations, the validity of which is thus often investigated. Their main focus is to make a preoperatively assessment and be the basis of a comparison with subsequent examinations, posttherapeutic especially.

The objective examinations are represented by the endoscopy of the nasal cavities, the anterior active rhinomanometry and the acoustic rhinometry, the nasal peak flow, the computed tomography (CT) scan of the nasal pyramid and paranasal sinuses. A special place must be given to the visual scale self-assessment of breathing made by the patient.

Although subjective, this measure is an excellent and very simple method of assessment of the functional impairment experienced by the patient so that it could be called “self-comparative.” Other more sophisticated methods belong to the research field.

We can compare the tests evaluating the consequences of nasal obstruction on the quality of life, often used during investigations. Nevertheless, their heavy nature limits the use in daily practice. A detailed examination will identify the medical, trauma, and surgical history, the medications used and the regular use of vasoconstrictors or the consumption of illegal drugs such as cocaine, the type of nasal obstruction, the aggravating circumstances and breathing improvement. The consequences of this obstruction on patient’s quality of life could be assessed by scores such as the visual analogue scale, the Nasal Obstruction Symptom Evaluation, the rhinosinusitis quality of life survey.

It is important to note the existence of problems with smell, epistaxis, rhinorrhea, cephalgia, as well as indirect signs, such as morning asthenia or nocturnal urination, as indications of possible sleep apnea (Epworth score).

Progressive local or general disease such as the Wegener disease or chronic diseases of the respiratory mucosa have to be excluded. Nasal morphology observation, nasolabial angle measurement and the Cottle maneuver represent the first step of the clinical examination by requesting the patient to self-assess on the visual scale the improvement obtained by lifting/rotating nasal tip and by the lateral stretching of the
nostrils, or even by the two techniques performed simultaneously. The patient is asked to breathe strongly and long in one shot, to observe the behavior of lateral nasal wall, the possible collapse of the middle one-third of the nose, the narrowing of alar cartilages or the tip region.

Moreover, we can again do the spacing Cottle maneuver and the cephalic rotation of the nasal tip while the patient inspires violently, so as to dynamically assess the role of these structures in the nasal obstruction, also simulating at the same time a possible therapeutic action on the valves or the morphology of the nose.

The anterior rhinoscopy can monitor the status and position of the anterior septum, the state of the triangulo-septal angle, the volume of the inferior turbinate heads, and the width of the pyriform aperture. The endoscopy of the nasal cavity then looks deeper into the posterior two-thirds of the septum, inferior turbinate tails, concha bullosa, the state of the choana, and rhinopharynx.

Thus, it is possible to observe nasal polyposis, a serous discharge or pus from the sinus, synechiae or sequelae as septal perforation. This diagnostic step is fundamental.

It logically precedes the therapeutic decision according to a rationalized decision process.

The therapeutic treatment of chronic nasal obstruction may be very simple but can quickly become problematic when the surgical solutions are disproportionate in relation to the complaints, and therefore quickly refused by the patient.

Thus, a turbinoplasty and/or a septoplasty are by far the most frequent proposals that solve most of nasal obstructions in adults. The more complex situations often appear after septoturbinoplasties, which have proven to be ineffective, and even sometimes aggravating.

A fine semio logical analysis is necessary and must identify the reason for the failure to be able to propose an effective solution in a patient who has become uncooperative after a first failure.

It is most often in these particular situations, or after primary rhinoplasties that we are able to recognize nasal stenosis due to a narrow pyriform aperture, a collapse of nasal valve or lateral wall of the nose. The diagnosis of empty nose syndrome after radical turbinectomy poses a real therapeutic problem, however it must be always balanced with the stenorrhinia or the nasal valves collapse; indeed, many of empty nose syndromes are associated with these other local abnormalities whose treatment will be able to improve patient airflow.

The diagnosis of nasal valve collapse or stenorrhinia are not evident if the surgeon is not prepared for these situations and if these etiologies are not systematically discussed at the initial assessment of a patient with chronic nasal obstruction. In practice stenorrhinia is found schematically in two clinical situations: constitutional primitives or secondary after rhinoplasty.

On one hand, it could represent a constitutional nasal stenosis in connection with a growth disorder of the premaxilla; semio logically, patients often present with a high arched palate and are positively improved by the Cottle maneuver.

With the CT scan on the coronal through the insertion of the inferior turbinate head, we distinguish the protruding frontal processes of the maxilla that narrows the nasal vestibule. The solution is either a lateral osteotomy or a limited osteotomy of the frontal process including the bone insertion of the inferior turbinate head.

On the other hand, stenorrhinia after secondary rhinoplasties is directly linked to the performance of too low lateral osteotomies that induces the medialization of the inferior turbinate head insertion reducing the airflow in nasal vestibule. Webster had described a triangle to respect on pyriform aperture when performing lateral osteotomies. The diagnosis and treatment are exactly identical in constitutional stenorrhinia. The great discussion on the nasal valves is a subject still not completely resolved in the international literature.

Some confusion reigns on the definitions of the nasal valves and sometimes on their existence.

However, generally an internal valve mainly in relation to the septo-triangular cartilage unit, and an external valve essentially muscular and nasal are recognized.

In our opinion, it is also necessary to distinguish an extrinsic nasal structure directly related to the bony pyriform aperture containing the nasal spine, the floor edge of nasal cavity and the frontal process of the maxilla with the insertion of the inferior turbinate head.

According to Daniel et al, the analysis of the lateral nasal wall leads to the conception of a composite lateral valve formed by the bony lateral nasal walls, the lateral fibrous triangle, the lateral extension of the upper lateral cartilage and the sesamoid bones of the lower lateral cartilage, and by the lateral muscular part of the nostrils. These anatomical structures converge laterally to form a composite structure whose medial collapse can act as etiology of dynamic nasal obstructions.

The therapeutic solutions proposed in these collapses of the nasal valves most often require sophisticated surgical procedures which modify the appearance of the nose sometimes favorably in the case of certain spreader grafts, often unfavorably in case of techniques of lateral wall reinforcement (alar batten grafts) or dilation of the internal valve (butterly grafts), which enlarge the nose laterally and/or flatten the middle third of the nose and alar cartilages.

In the therapeutic field of nasal surgery, a simple, rapid, noninvasive, and effective solution in these situations has not been reported yet. An original solution of lateral dilation of the nose was proposed. The Cottle maneuver was reproduced by fixing threads to the nasal valve and by pulling them toward the orbital rim laterally and at the top where these threads are secured by screws anchored in the bone. This clever but difficult technique had not great success. Here, we propose a particularly simple and inexpensive technique, with a rapid learning curve, which may be performed under local anesthesia.

The idea to this novel technique came in December 2011 after a demonstration in Moscow of new threads manufactured in the United States with Food and Drug Administration (FDA) and European Economic Community (EEC) approval. These threads are absorbable and designed with cone anchors.
Patients and Methods

A prospective study was conducted from January 2012 to December 2013 in Nice and Barcelona. The aim of this study was to determine the effectiveness and validity of a new technique for the chronic nasal obstruction treatment. A total of 45 patients have undergone this technique during this 2-year period. Written consent was obtained for all patients included in this study, whose photos are used and presented in this article.

The study includes consecutive 45 cases of nasal suspension by directional self-retaining threads in patients with chronic nasal obstruction. The age of patients ranged between 24 and 70 years (average 45 years). The gender ratio was 1:1.

Selection of Patients

The patients selected were adults older than 18 years with chronic nasal obstruction resistant to medical treatment or recurring after the end of medical treatment; these patients could have had previous surgery, however, the type of surgery was not a decisional factor in the inclusion.

Improved nasal ventilation with the Cottle maneuver had to be shown according to an improvement of at least two decimals on a visual scale of 0/10 to 10/10.

The exclusion conditions of the patients were as follows: age older than 90 years (one patient), the presence of chronic disease (one patient), and coronary cardiovascular disease (one patient).

All patients underwent a clinical examination, photos (the seven basic pictures of rhinoplasty and dynamic photos of breathing), a bilateral fibroscopy of the nasal cavities (pediatric fiberoptic flex of 2.7 mm, Karl Storz ORL, Tuttingen, Germany), a functional assessment of nasal ventilation and rhinosinusal CT scan. The functional assessment was performed in Barcelona by the pneumology team, using acoustic rhinometry and/or nasal peak flow; moreover in Nice, using active anterior rhinomanometry (ATMOS equipment, Lenskirch, Germany).

All patients were subjected to a visual scale to evaluate breathing individual perception before and after the procedure, therefore assessing the airflow improvements obtained.

Information to the patient was given using pictures of a previous patient undergoing live surgery in Barcelona (Silhouette Lift International Congress April 2012) who agreed with his image and/or video release.

Functional results were evaluated according to the same techniques of functional assessment at regular intervals, that is, 1, 3, 6, 12 months, and then provided for every 6 months.

Patients were questioned at the end of the procedure and during postoperative monitoring to assess morbidity. They were asked to report on bleeding, local pain, bruising, swelling, discomfort in relation to the presence of threads and cones, along with discomfort in wearing glasses.

They were also asked whether they would again undergo the procedure in the event of loss of effectiveness.

Anesthetic Procedure

Overall 25 Patients underwent strict local anesthesia, 11 underwent general anesthesia with laryngeal mask and 9 underwent neuroleptanalgesia, after free choice by the patient of anesthetic options.

All patients were treated in day surgery, their average length of stay in the clinic or office was 3 hours.

Required Equipment

The equipment required for the procedure are as follows:

- For the patient: A cap is necessary, secured with adhesive paper at the hairline; skin disinfectant (lodate pirolidone or chlorhexidine depending on the case) and a small sterile operating area.
- Operating table: A sterile table area; instrumentation: one short nasal speculum, one needle holder, one pair of thread scissors, one Gillies hook, sterile compresses, oxygenated water in a cup; lighting by either frontal or sclerotic light; local anesthesia with syringe of 2 mL and two needles (one of 30 gauges and one long and thin retrobulbar type); and dermatographic pencil.
- Medical staff: One assistant or nurse is desirable but not essential.

Operating Technique

Situation 1: Exclusive suspension of the nasal valve.

The patient is placed in supine position; the skin is disinfected with betadine or chlorhexidine. Local anesthesia is applied on the entry point, exit points, and on the needles path with 1% Xylocaine (Labo Abbvie, Aprilia [LT], Italy) with 1:100,000 adrenaline.

Later a skin puncture (prehole) is performed with a pink needle of 14 gauges through the skin and subcutaneous tissue of the nasal base until bony contact.

The needles have to be curved before their introduction so as to anticipate the curvature of the nasofrontal hollow, moreover to allow the correct passage in the superficial muscular aponeurotic system (SMAS) of the lateral parts of the nose and their exit at the point determined before the procedure.

The technique consists in different phases: introduction of the first needle through the prehole, perpendicular to the skin until bony contact; then orientation in the soft tissues of the lateral wall of the nose; the progression of the needle is followed by palpation with the operating finger in the same way of a lateral osteotome (Figs. 2 and 3). The needle must exit caudally at the marginal caudal edge of the lower lateral cartilage (LLC) at the level of the external third, under the first sesamoid cartilage.

After its release, the needle is retrieved with the needle holder and the cones are introduced from the basis of the nose, pulling the thread down until the full transition of all ipsilateral cones. Dragging the skin behind, the cones could slide by draping the nasal skin as appropriate.
A second needle is introduced contralateral through the same hole following the same procedure. The threads are symmetrically strained, producing an immediate valve enlargement, instantly felt by the patient in the event of a procedure under local anesthesia. The external remaining part of the threads is finally cut. The new position of the skin is maintained using adhesive paper for 2 days from the tip to the base of the nose. In the postoperative setting, the external skin of the nose is cooled for the next 2 hours to limit postoperative edema and bruising.

No more dressing is required. In the event that we decide to place two threads, we carry out the same procedure with the second thread, passing through the same previous skin hole made at the level of the nasal base and directing the second needle parallel to the first thread and exiting it at 2 mm in the nasal vestibule (two cases). The average duration of the threads placement is 15 minutes, while the entire procedure lasts on an average 35 minutes (from 25 to 45 minutes).

Situation 2: Association of suspension of the valve and rotation of the tip.

Two threads are necessary. They are introduced in W in reverse and then crossed over, following the same procedure as above, but following different ways.

The two threads are positioned symmetrically, crossing over each other at the midline to ensure the stability of the result overtime: one end comes out at the level of the valve and the other end through the columnellar skin just medial to the contralateral dome; the tension of the thread is achieved by raising the tip of the nose and pulling the thread caudally. The operator observes on the lateral view to assess the correct opening of the nasolabial angle as well as the correct tip position.

Results

A total of 45 patients have undergone the “nasal valve lift” technique since January 2012, however in this study
Functional results were considered in the first group of 16 patients with a medium follow-up of 14 months (range 12–16 months). Three patients received a mixed technique called “nasal lift” combining nasal valve lift and nasal tip cephalic rotation or nasal tip lift to open the nasolabial angle, using two threads, while four underwent the introduction of two threads to the valve. All patients were hospitalized in day surgery for an average duration of 3 hours. The recommence to work was possible the next day for all patients, some of them (three patients) immediately returned to their professional activity.

Postoperative morbidity was very limited: nasal and lower palpebral ecchymosis in two patients for 4 days; discomfort wearing glasses was claimed for 1 month in one case, unpleasant sensation of threads below skin for one patient. No pain has been reported. The ventilatory improvement was evaluated in all patients, except for one. The preoperative mean value of patients on the visual scale was 4.5/10 (range 2–6/10), while the postoperative was 8.0/10 (range 6–10/10). No negative result was reported. The minimum improvement was 15%, the maximum 200%, and the average improvement was 100%. The satisfaction index was 90% and 44 patients were willing to undergo the procedure again if necessary, in the event of losing the result obtained over the time. The patient who underwent a complete nasal lift combining nasal valve lift and nasal tip lift with rotation of the tip to open the nasolabial angle, were immediately very satisfied with the result with a measured improvement of the nasolabial angle of 10 degrees.

Discussion
In the pathophysiology context we should distinguish three main situations.

It is widely known that the closure of the nasolabial angle could be the cause of inspiratory air turbulence in the nasal vestibule with a loss of nasal airflow. The lateral collapse of the valve may be due to either a closure of the internal valve, a weakness of the external valve, or finally, a weakness of the lateral walls of the nose. Finally, the stenorhinia of skeletal origin. We set aside the infrequent situations of narrow pyriform aperture, vestibular synechiae, and thick columellar base that obstruct nasal cavities airflow without excluding that the technique proposed could produce an improvement.

The aim of using directional anchoring threads is to improve the inspiratory flow by opening the nasal valves, ensuring if necessary the cephalic rotation of the nasal tip and stiffening of the lateral nasal walls. The thread is positioned...
on the nasal base in the manner of a horse’s saddle: a passive support which stabilizes and avoids the slipping of the thread downward. The passage on each side in the nasal SMAS that is in the soft tissues between the periosteum and deep dermis gives the support and the anchorage of the cones in the ligaments of the nose. The point of emergence could be the plica nasi for an opening of the internal valve (Fig. 4); however, a more complete action covering not only the internal valve but also the external valve and the lateral nasal wall is more effective.

Indeed, the existence of four cones at cephalic anchoring allows simultaneous tension of both sides, laterally and upward, reproducing the result obtained with the Cottle maneuver.

**Regarding the Material Used and Its Positioning**

We currently use absorbable threads which have the advantage to be disposable and to avoid leaving permanent materials. The cone threads are made of polylactic acid and sold with FDA and EEC approval. Perfectly identical to the suture threads already used, they do not pose any problem of intolerance or allergy.

Their configuration with four cones on each side or eight cones is designed in such a way to be self-retaining, as hooks disposed in opposition.

The cones are effectively arranged in two sets of four separated by 1 cm smooth thread.

No adhesion to the skin must be made. Thus positioned, the thread acts by retracting the nasal valve toward the nasal base, self-retained by the eight cones. No stitches, no sutures, no other material or dressings are necessary except the adhesive paper for 2 days to allow fibrosis beginning. On the other hand, the need of threads anchorage on the nasal SMAS does not allow using this technique in surgical rhinoplasty. A mini-rhinoplasty without lateral elevation of the soft tissues can be associated with a “nasal valve lift” passing through the intact tissues.

**Regarding the Technique Used**

For the problems posed by the closure of the nasolabial angle, two solutions are proposed: either the rotation of the nasal tip, or the filling of the nasolabial angle with inert materials of varying natures positioned in front of the premaxilla and the anterior nasal spine, or a combination of the two techniques. The rotation of the nasal tip can be surgically obtained during rhinoplasties. After the initial separation of the external skin which allows the cephalic movement of cartilages forming the nasal tip, one or several techniques may be proposed: cartilage resection of the triangulo–nostril junction, reduction of the caudal edge and the anterior angle of the quadrangular septal cartilage, “tongue in the groove” described by Kridel et al., section of the septi nasi depressor muscle. All of these procedures are invasive and require treatment in a specialized surgical environment. The positioning of self-retaining directional anchoring threads ensures a certain cephalic rotation of the nasal tip. The threads must meet two requirements: on one hand, they must provide effective anchoring to allow the rotation of cartilage and fight the elastic effect; on the other hand, they must maintain the result in a sustainable way.

The anchoring is ensured by the presence of cones on the nasal SMAS region. The SMAS has been described as composed of two layers, superficial and deep, which surround the cartilage and the nasal valve; thus, the cephalic tension of the SMAS produces a cephalic rotation of the nasal tip. Regarding the sustainability, it could be compromised by a poor stability of the attachment to the base of the nose or a gradual sliding down of the threads on nasal bones. To avoid this phenomenon, we propose the placement of two threads arranged in V in reverse and crossed over the midline according to an angle open enough to avoid any caudal slipping of the support.

When patients require treatment for a too closed nasolabial angle, the technique that we propose is interesting for several reasons. It allows a real rotation of the nasal tip that was measured 10 degrees in our patient (Fig. 5). For its lack of invasiveness, it can either be performed alone or as part of a medical rhinoplasty for aesthetic but also functional purpose. Filler products such as autologous fat or cross-linked hyaluronic acid or calcium hydroxyapatite can be combined and positioned in front of the nasal spine. In some cases, botulinum toxin injection into the superficial fascia of oribicularis oris muscle and/or into muscle depressor septi nasi can be associated.

The lateral collapse of the nasal wall is most often in relation to the weakness of it, which is not resistant to the inspiratory pressure of the airflow entering the nostrils according to the Venturi effect. The nonsurgical techniques for opening the nasal valve involve the introduction of removable orthotic devices, which can be arranged either on the external skin or in the nasal vestibule. The external orthotics are adherent to the skin and are most often used in sports while internal orthotics are often proposed for nocturnal nasal obstructions. Their tolerance is poor and their use of short duration; the patients often ask for more sustainable and less restrictive procedures that we were not able to offer them up till now.

The action of suspension by threads that we present here will produce an internal enlargement of the lateral wall of the

![Fig. 4](image-url) The plica nasi as a point of emergence of the threads to open the internal nasal valve.
nasal vestibule, in the manner of nostril dilators; in the other side they present the advantages of sustainability and tolerance.

Regarding the Surgical Procedure

The surgery of nasal valve represents a real decisional problem: the lateral collapse of the nasal wall and valves requires complex procedures of repair.

Three major types of techniques have been described: (1) those that open transversely the triangulo-septal angle, (2) those that aim to stabilize the lateral wall and the external valve, and (3) those that plan to open the nasal vestibule laterally and to reproduce the effects of the Cottle maneuver.

Without repeating each technique, all of them share as common point the need to involve a bone or cartilage graft and the placement in the weakness area: spreader grafts, alar batten grafts or butterfly grafts, as well as most often an open rhinoplasty type incision.

The technique of suspension by self-retaining directional anchoring threads offers two major advantages: the opening of the internal aperture; on the other hand support and increased rigidity of the lateral wall that no longer suffers the Venturi effects of inspiratory depression.

Regarding the Durability of the Result

The expected durability of the result is 14 months on an average, which corresponds to the normal resorption of the polylactic acid thread according to the standards of the manufacturer, which corresponds to the medium follow-up of 14 months considered in our study. No patient has observed loss of effectiveness during evaluation on the visual scales and the measures objectively performed do not highlight a decrease of the result. Although, the number of patient remains limited and the follow-up short, we can assert that these results on durability are encouraging.

In addition, the threads and the polylactic acid cones produce fibrosis, which can hold the result beyond threads of normal duration.

On the other hand, assuming that these results are encouraging in term of tolerance and efficacy, the durability can be enhanced using nonabsorbable threads with polylactic acid cones, already used with FDA and EEC approval for facial suspension for aesthetic purposes or in facial paralysis.

Conclusion

A prospective study has been performed to assess a new technique of nasal lift. This is a new noninvasive technique for the treatment of nasal obstruction and nonsurgical rotation of nasal tip using self-retaining directional anchoring threads. Performed under local anesthesia, the procedure lasts approximately 35 minutes. The toleration and efficacy are excellent. The durability, at this stage of the evaluation is very good at 14 months (range 12–16 months). It can provide a therapeutic solution filling a void between poorly tolerated external orthoses and invasive surgery requiring grafts, consequently rarely offered to patients.

However, the management of nasal obstructions requires a precise therapeutic and diagnostic approach. The application of a new technique to poorly selected indications must be avoided.

Furthermore, it is necessary to make sure of the nasal valve role in nasal obstruction described by the patient. A detailed clinical examination including the Cottle maneuver, at least one objective measure by peak flow and a visual scale evaluation are the basis of nasal valve lift technique.

The rotation of the nasal tip is promising in a medical rhinoplasty context. However, it requires a more exhaustive study with significant follow-up. The indications are currently represented by the moderate closures of the nasolabial angle with a default rotation of nasal tip. The "nasal lift" can

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**Fig. 5** Application of the technique in case of moderate closure of the nasolabial angle. Measurements of nasolabial angle, double break, dome and nasal length. (A) Nasolabial angle measures 92 degrees. (B) Postoperatively, it is demonstrated that the rotation of the tip and the opening of the nasolabial angle now measures 102 degrees.
therefore combine the opening of the valve or “nasal valve lift” and the rotation of nasal tip or “nasal tip lift.” Prospective scientific studies on a larger number of cases and a more prolonged follow-up will help to evaluate the real contribution of this technique which is undoubtedly still perfectible.

References

PRFM Enhance Wound Healing Process in Skin Graft

Mirta Reksodiputro, MD, ORL, PhD1 Dini Widodo, MD, ORL, PhD1 Jenny Bashiruddin, MD, ORL, PhD1 Nurjati Siregar, MD, MS, PhD2 Safarina Malik, DVM, MS, PhD3

1 Department of ENT, Faculty of Medicine, University of Indonesia, Jakarta, Indonesia
2 Department of Pathology Anatomy, Faculty of Medicine, University of Indonesia, Jakarta, Indonesia
3 Department of Biology Molecular, Eijkman Institute, Jakarta, Indonesia

Address for correspondence Mirta Reksodiputro, MD, ORL, PhD, Department of ENT, Faculty of Medicine, University of Indonesia, Jl Diponegoro No 71, Jakarta, Dki Jakarta 10413, Indonesia (e-mail: citamirta@yahoo.com; ina@eijkman.go.id).


Abstract

Facial plastic and reconstructive surgery often used skin graft on defects that cannot be covered primarily by a local flap. However, wound healing using skin graft is slow, most of the time the graft is contractured and the take of graft is not optimal. Platelet rich fibrin matrix (PRFM) is a new generation of concentrated platelets that produce natural fibrin and reported to speed up the healing process. Application of PRFM in the skin graft implants is expected to increase the survival of the graft. We used porcine as animal models to elucidate the effect of autologous PRFM on wound healing in full-thickness (FTSG) and split-thickness (STSG) skin grafts. Survival level of the skin graft was determined by using ImageJ software based on the formation of collagen type 1 and graft take. We observed that the use of PRFM in FTSG and STSG increased type 1 collagen formation. We also found that PRFM addition in STSG gave the best skin graft take.

Keywords

► PRFM
► skin graft
► wound healing
► porcine

Background

Development of tissue engineering has created lots of biological products that help the acceleration process of wound healing,1 which have significant effects on surgery results, especially in the otorhinolaryngology head and neck plastic reconstruction. Tissue engineering generally needs additional growth factors to be assimilated into the cell to increase the potential for new tissue regeneration.2 One of the most used biological products for wound healing process is platelet rich plasma (PRP). PRP is a concentrated autologous platelet as the source of growth factors. Alpha-granules released from the platelets are known to contain various growth factors required in the process of wound healing. The growth factors are released during the occurrence of platelet activity.3 However, PRP does not provide optimal outcome, because of its liquid form and also the development process that uses xenologous bovine thrombin. Besides, the release of growth factors from the platelets in PRP occurs only at once in the beginning of the application. A different form of autologous platelet preparation has currently been developed, namely, platelet rich fibrin matrix (PRFM), which has a denser and pliable structure.4 PRFM is a new generation of platelet concentrate that produces natural fibrin in which the platelets are dispersed. Based on its morphology, PRFM also acts as a scaffold that helps localize the growth factors. As a source of autologous growth factors, it is expected to decrease the length of hospitalization through optimized wound management.5,6 Further, PRFM has been reported to be useful for other reconstructive surgery.

For otorhinolaryngology head and neck plastic reconstruction, a skin graft is often applied to defects that cannot be covered primarily by local flap. Depending on the skin graft thickness, there is a possibility of contracture and the less optimal healing process. According to its thickness, the skin graft can be classified as split-thickness skin graft (STSG) and full-thickness skin graft (FTSG). In general, FTSG is used for face and ear areas to obtain thickness appropriate with the
wound defect, because of its texture and color that is more suitable as compared with STSG. In terms of revascularization process, the survival of FTSG is not as good as STSG. However STSG contracts more easily as compared with FTSG, the thinner the STSG the more chance of contracture occurs.7-9 As PRFM have been reported to accelerate the wound healing process, the possibility that PRFM could overcome STSG contracture needs to be explored further. The use of PRFM has proven its ability to accelerate the wound healing process such as ulcers.10 Application of PRFM on skin graft implants is expected to increase the survival quality of the graft. A commercial device to produce PRFM is currently available, but is costly. Furthermore, mechanism of PRFM in accelerating wound healing process of skin graft is still unproven. Available studies only show in vitro evidence, which leads to the role of growth factors.

**Objective**

The objective of this research is to evaluate the effect of PRFM in accelerating the wound healing process of skin graft. The role of PRFM in the physiological process of skin graft wound healing was evaluated microscopically based on the development of collagen type 1 and macroscopically based on the morphological changes of the skin color at days 14 and 30.

**Methods**

**Animal Model**

Five Sus scrofa porcines (1 male and 4 females), aged between 6 and 8 months with body weight between 27 and 40 kg were used in this research. This research was conducted at The Animal Hospital of Faculty of Veterinary Medicine, Bogor Agriculture University, under the supervision of a veterinarian. Ethical approval was obtained from Animal Care and Use Committee (ACUC), Veterinary Teaching Hospital. During harvesting and implantation of skin graft, porcines were under general anesthesia. For 30 days, treatment of wound was conducted to prevent infection and binder band was used to protect skin graft.

**Skin Graft**

Four rectangular specimens, two FTSGs and two STSGs, were harvested from the back area of the porcines. Blade no. 10 was used to harvest FTSG, while a 0.018 in. dermatome was used to harvest STSG.

**Platelet Rich Fibrin Matrix Preparation**

Around 8 mL of citrate blood in a RegenKit tube (RegenLab, Le Mont, Switzerland) was centrifuged at 1,500 g for 5 minutes to obtain three layers, which were red blood cell sediments at the base of the tube, gel that was part of the RegenKit tube, and plasma above the gel. Plasma layer consisted of two parts; the one adjacent to the gel was PRP and above PRP was platelet poor plasma (PPP). In this research, both PRP and PPP layers were mixed until homogeneous to obtain a sufficient volume to produce PRFM. This mixture of PRP and PPP was defined as PRP in this research. Preparation of PRFM was a continuation of PRP preparation, which was done by modifying Fibrinet method10; 25 mM CaCl2 was was added into the PRP followed by 1,800 g centrifugation for 60 minutes. Coin-shaped sheet PRFM with a diameter of 25 mm was obtained.

In each step, platelet was counted from whole blood, PRP, and PPP using automatic cell counter Celtaclα (Automated Hematology Analyzer MEK-6450, Japan).

**Platelet Rich Fibrin Matrix Application**

After harvesting, grafts were reimplanted at its original location, with or without PRFM application. The coin-shaped sheet PRFM was applied at the center of the bed underneath the skin graft. Graft was fixated by tight over suture for 7 days postsurgery.

**Evaluation of Collagen Type 1 Density**

To evaluate collagen type 1 density tissue specimens were obtained by biopsy using 6-mm punch biopsy that covers skin graft and bed. Survival rate of the skin graft at days 14 and 30 was microscopically evaluated by measurement of collagen type 1 density with picrosirius red staining at ×40 magnification using ImageJ software. The results were reported as percentage of type 1 collagen density per field of view.

**Macroscopic Evaluation**

Survival rate of the skin graft at days 14 and 30 was macroscopically evaluated by assessment of color changes of the skin from photographic documentation using Canon Ixus 900 Ti digital camera (Canon USA, New York, NY). A 3 × 3 cm area on the skin graft was marked before taking photograph. During this process each photo of treatment was separated one from the other according to markers that was made earlier. Photo results were processed and analyzed using ImageJ software, by assessing the color of each skin graft. Conversion of photograph results to ImageJ interpretation was done independently for each treatment to prevent factors that influenced biased assessment. Skin color closer to normal skin was interpreted as better survival.

**ImageJ Evaluation**

Captured photos in JPEG format were imported into ImageJ software. This software was then used to evaluate photo results, as well as show, edit, process, save, and print pictures with density rate of 32 bits. ImageJ software was able to calculate statistic values of widespread and image density in pixels.11

**Evaluation of Extracellular Matrix**

Biopsies of STSG were conducted on day 30 to analyze cellularity and extracellular matrix that represent types 1 and/or 3 collagen. The samples were stained with hematoxylin-eosin and observation was focused on the area of graft and bed.

**Results and Discussion**

Porcines were chosen as experimental animals because of its skin anatomy similarity to human skin (epidermal, dermal,
and skin color). The mean of porcines peripheral blood count was within normal limit with platelet count of $567,400 \pm 82,150/\mu L$ (Table 1). During implementation of the skin graft there were some difficulties in treating the porcines skin graft wound, because naturally porcines were not hygienic. To maintain cleanliness of wound and fixation of graft on place, binder band was dressed on porcines and observed for 30 days. Every time biopsy was conducted, a fresh clean one replaced the previous binder band. If before biopsy the binder band gets dirty, it would also be replaced. No infection occurred during 30 days of observation.

PRP that was used for PRFM preparation was obtained from centrifuging 8 mL citrate blood at 1,500 g for 5 minutes at room temperature (RegenLab centrifuge). About 6 mL PRP was transferred into a sterile 30 mm diameter plastic Wheaton container, then CaCl$_2$ 25 mM was added and centrifuged immediately using Beckman CS-6R centrifuge (Beckman Instruments, Inc., Fullerton, CA) at 1,800 g for 60 minutes.

Using this method, around 25 mm diameter coin-shaped PRFM were obtained (Fig. 1). A slight shrinkage of PRFM that can be seen might have been caused by contraction that occurred during the formation of fibrin fiber. The produced PRFM were more dense and pliable, resembling a fascia layer and could be stitched. The advantage of this character made PRFM act as a scaffold, which would serve as the collecting place of inflammatory cells in the wound healing area. This coin shape was suitable for application in skin graft bed. Other than that, this method could be used for PRFM preparation that could be applied in clinics, such as for ulcer treatment and sockets filling in dentistry, as well as for face implant if applied together with autologous fat.

There were several phases in wound healing process. The survival of skin graft healing can be seen starting at day 14. The effect of PRFM application in accelerating the wound healing process of skin graft was evaluated microscopically based on the development of type 1 collagen and macroscopically based on the skin color changes, which were obtained at days 14 and 30.

In the proliferation phase, fibroblast cells synthesized type 3 collagen that would be replaced by type 1 collagen, which will make the wound healing area stable similar to normal skin tissue. When extracellular matrix in this wound healing area got closer to its natural condition, the number of fibroblasts was decreased by undergoing apoptosis, will be replaced by collagen. On both FTSG and STSG at day 14, the highest collagen density was seen on skin graft with PRFM. Continuing with the maturation phase, at day 30 the type 1 collagen density increased. The highest type 1 collagen density was observed in skin graft treated with PRFM for both FTSG and STSG at day 30 (Fig. 2). Type 1 collagen formation at days 14 and 30 in all FTSG was observed to be lower than in all STSG (Fig. 3). Since the type 1 collagen in STSG-PRFM had the highest density it could be assumed that wound healing in STSG-PRFM could reach normal skin condition faster than the other treatments.

STSG has been known to heal faster than FTSG. However, STSG has a tendency to be contractured. Hematoxylin-eosin that stained both graft and bed showed that the extracellular matrix of STSG-PRFM appeared to be much more dense and the cellularity was observed to be much less as compared with STSG-control (Fig. 4). More extracellular matrix and less cellularity are indicators of a faster healing. In addition, more extracellular matrix means that there were more collagen, and dense collagen means reduced chance to developed contracture.

A successful skin graft wound healing can be determined not only from type 1 collagen density, but also from graft survival. A good survival of skin graft was marked by the graft color. The more the skin color resembled normal skin the more success of skin graft healing, indicating a good take. According to both types of graft with different treatments, it appeared that the highest increased of survival at days 14 and 30 was seen in graft with PRFM. This indicated the positive role of PRFM in influencing survival of graft (Fig. 5). Thus for skin graft survival, STSG was better than FTSG except in treatment with PRFM at day 14. Differences in survival between these FTSG and STSG are obviously seen at day 30 (Fig. 6).

There are lots of factors influencing wound healing process that was not investigated in this research, among others angiogenesis process that play a role in providing vascularization for graft to fulfill the nutritional needs would be fulfilled. It is well established that the vascularization process of STSG is better than FTSG, therefore, STSG has a higher success rate in wound healing process. This explains why in this research the survival rate percentage of

<table>
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<th>Characteristic of Porcine</th>
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<tr>
<td>Age (mo)</td>
<td>6.80 ± 1.09</td>
</tr>
<tr>
<td>Sex</td>
<td>1 male and 4 females</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>32.60 ± 6.80</td>
</tr>
<tr>
<td>Platelet count (/μL)</td>
<td>567,400 ± 82,150</td>
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STSG was better than FTSG. The average survival rate of FTSG on each day 14 and 30 did not show large difference between control and PRFM treated. Similar to FTSG, the average STSG survival rate at days 14 and 30 also did not show much difference between control and PRFM treated. The survival rate from day 14 until day 30 was calculated, and the result showed that a sharp increase was observed on STSG-PRFM (53.87%). This sharp increase indicated an acceleration of wound healing on STSG-PRFM (Table 2), showing a better skin graft wound healing.

Wound healing occurs through several stages starting from hemostasis, inflammation, proliferation, and maturation. The hemostasis stage occurs immediately after graft was harvested (FTSG and STSG) and still continue after reimplantation of graft in 30 minutes, with previous treatment to the base of graft (bed). It is well established that among others, endogenous growth factors improved wound healing. It is also known that the amount of growth factors might vary between individuals. To prevent the influence of varied endogenous growth factors, in this research, skin grafts with various treatments was conducted in one animal at one location, therefore these endogenous factors could be disregarded. Treatment toward each wound was equal.

In conditions that need larger skin graft, usage of FTSG is not possible; therefore STSG will become the only choice despite frequent contractures. Application of PRFM resulted in higher type 1 collagen density and survival rate, thus there

<table>
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<tr>
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<th>Day 14</th>
<th>Day 14 IMAGEJ</th>
<th>Day 30</th>
<th>Day 30 IMAGEJ</th>
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<th>DAY 14 IMAGEJ</th>
<th>DAY 30</th>
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Fig. 2 ImageJ analysis of type 1 collagen density of (A) FTSG and (B) STSG. It is shown that collagen type 1 density of FTSG and STSG with platelet-rich fibrin matrix application is higher than control. Increasing density at days 14 to 30 was seen. FTSG, full-thickness skin graft; STSG, split-thickness skin graft.

Fig. 3 Comparison of collagen type 1 percentage between FTSG and STSG. According to the treatment at day 14 (left) and at day 30 (right). FTSG, full-thickness skin graft; STSG, split-thickness skin graft.
is possibility that it might reduce the occurrence of contracture.

We concluded that in this study PRFM played a role in wound healing. Acceleration of wound healing would allow shorter waiting period for follow-up that might be required in several reconstruction surgeries. The wound that is being studied in this research was a noncomplicated wound that heals normally. However, in chronic wound or wound with

![Fig. 4](image)

**Fig. 4** Comparison of extracellular matrix between STSG-control (left panel) and STSG-PRFM (right panel). Shown are the biopsy graft and bed stained with hematoxylin-eosin. Extracellular matrix is the area that has no nucleus. The extracellular matrix in STSG-PRFM appears to be denser than STSG-control. STSG, split-thickness skin graft; PRFM, platelet-rich fibrin matrix.

![Fig. 5](image)

**Fig. 5** ImageJ of skin graft color of (A) FTSG and (B) STSG. It is shown that percentage of natural skin color of STSG with PRFM at day 30 is highest. Increasing percentage at days 14 to 30 was seen. FTSG, full-thickness skin graft; STSG, split-thickness skin graft; PRFM, platelet-rich fibrin matrix.
deficiency such as diabetic ulcer or cancer chronic wound, longer wound management is needed due to lower chance to heal completely. These kinds of wound need more growth factors to help the healing process. PRFM addition would improve the condition of the wound, in particular by providing growth factor in the wound environment that help accelerate the wound healing process, resulting in cost-effective wound management.

![Comparison of percentage of skin graft survival between FTSG and STSG.](image)

**Fig. 6** Comparison of percentage of skin graft survival between FTSG and STSG. According to the treatment at day 14 (left) and day 30 (right). FTSG, full-thickness skin graft; STSG, split-thickness skin graft.

<table>
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<th>Table 2 Survival rate of FTSG and STSG</th>
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<td>Treatment</td>
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<tr>
<td>FTSG</td>
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<td>PRFM</td>
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<td>STSG</td>
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<td>PRFM</td>
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Note: d is the difference in survival between days 14 and 30.

References

New Flap for the Reconstruction of the Perinasal Region

Fatih Doğan, MD1 İrfan Özyazgan, MD2

1Department of Plastic, Reconstructive and Aesthetic Surgery, Faculty of Medicine, Adıyaman University, Adıyaman, Turkey
2Department of Plastic, Reconstructive and Aesthetic Surgery, Faculty of Medicine, Erciyes University, Kayseri, Turkey

Address for correspondence Fatih Doğan, MD, Department of Plastic and Reconstructive Surgery, Faculty of Medicine, Adıyaman University, 02200, Turgutreis, Adıyaman, Turkey (e-mail: fatihdogan.prec@gmail.com).


Abstract

Various reconstructive methods ranging from secondary healing to free flap applications are used for the reconstruction of perinasal defects caused by trauma or tumor surgery.1–8 The method to be used for the reconstruction of this region is chosen considering many factors because of specific determining structures. The number of studies on the subcutaneous tissue and vascular configurations of this region are gradually increasing along with the accumulation of knowledge in this region. Herein, we describe the nasal superficial musculoaponeurotic system–pedicled island skin flap for the reconstruction of the nasal tip, supratip, lateral nasal margin, and infraorbital area. The described skin flap was performed for defects resulting from basal cell carcinoma excision in all the patients. Of the patients, 12 were females and 5 were males. The mean age was 67.8 years (range, 56–82 years). All patients were operated on under general anesthesia. The flap donor areas were closed primarily. None of the patients developed flap necrosis. Although mild edema and venous insufficiency were observed in the flaps in the acute period only in patients who underwent nasal tip reconstruction, these improved during follow-up. In the operated patients, no problem was observed in the donor area and nasal dorsal skin. The nasal superficial musculoaponeurotic system–pedicled island skin flap which we describe for the perinasal area reconstruction is a safe, easily performed and versatile flap. The multidimensional use of this flap together with a relatively easy reconstruction plan and surgical procedure would be effective in flap choice.

Keywords

► nasal reconstruction
► SMAS flap
► island skin flap

Various reconstructive methods ranging from secondary healing to free flap applications are used for the reconstruction of perinasal defects caused by trauma or tumor surgery.1–8 The method to be used for the reconstruction of this region is chosen considering many factors because of specific determining structures. As the perinasal region is located in the central aspect of the face, an aesthetic outcome is aimed at and thus single-session methods are preferred by considering topographic aesthetic units. The number of studies on the subcutaneous tissue and vascular configurations of this region are gradually increasing along with the accumulation of knowledge on the topographic aesthetic units of this region. Studies have demonstrated that the three-dimensional soft tissue structure of the external nasal region9 consists of skin, a superficial areolar layer, fibromuscular layer, deep areolar layer, and perichondrium. While local flaps are successfully used for the reconstruction of small defects because of the rich vascular structure of the region, options are limited particularly for the reconstruction of medium and large defects. In this study, the superficial musculoaponeurotic system (SMAS)-pedicled island skin flap is described for the reconstruction of defects in the nasal tip, supratip, infraorbital area.
orbital area, and lateral nasal area. In the literature, although there are reports on the reconstruction of defects in the nasal region using SMAS and skin grafts, the SMAS-pedicled island skin flap is defined for the first time.

**Surgical Anatomy**

While the skin in the dorsum of the external nasal region is thin and pliable, it is thick and attached to the underlying nasal skeleton in the nasal tip and alar area. Although the nose is thin in the cephalic aspect of the lateral nasal wall, it becomes thick in the caudal aspect. There are four layers between the skin and bone: a superficial areolar layer, fibromuscular layer, deep areolar layer, and periosteum/perichondrium. The fibromuscular layer contains nasal muscles and the nasal musculoaponeurotic system and shows continuity with facial SMAS. The transversalis nasalis is the muscle found in the SMAS (without including the tip, ala, and columella) in the nasal dorsum. The deep areolar layer lies between the nasal SMAS and periosteum/perichondrium and contains major superficial blood vessels.

The internal and external carotid system forms the superficial arterial system of the nose (Fig. 1). Blood supply to the external nasal region is provided by the lateral nasal artery, angular artery, dorsal nasal artery, and columellar artery. Although the lateral nasal artery mainly arises from the frontal artery, it may sometimes also arise from the superior labial artery. Angular arteries may take root in the lateral nasal artery or may directly extend as a branch of the facial artery. Columellar arteries arise from the superior labial artery, which is the branch of the facial artery. The dorsal nasal artery mainly arises from the ophthalmic artery, which is included in the internal carotid system, and is anastomosed with the external carotid system in the external nasal area. The external nasal vascular network is formed by the branches of arteries listed above and the anastomoses among them.

**Patients and Methods**

Reconstruction was performed using the SMAS-pedicled island skin flap in 17 patients (Table 1). The defect areas of the patients were the nasal tip, supratip, lateral nasal margin, and infraorbital area. Flap size varied between 24 × 20 mm and 35 × 25 mm. Nasal SMAS-pedicled island skin flap was performed because of basal cell carcinoma in all patients. Of the patients, 12 were females and 5 were males. The mean age was 67.8 years (range, 56–82 years). The lesions were excised with surgical borders (5 mm) and the borders were verified to be clear-intact by the frozen section procedure. Reconstruction was planned after all margins of the defect were freed from the tumor. All patients were operated on under general anesthesia. Flap donor areas were primarily closed. In addition, soft-tissue aesthetic outcome was assessed by an independent examiner using visual analog scale (VAS) at 6 months following the surgery.

**Surgical Technique**

Blood control was performed in the defect area which occurred after the excision of basal cell carcinoma in the perinasal region, a skin island was drawn in the nasal radix area in a size appropriate for the defect, and reconstruction was planned. Subsequently, the inferior margin of the planned flap was incised up to the subdermal plane. Thereafter, the nasal dorsal skin area in the inferior aspect of the flap was elevated in the subdermal plane. At the superior and both lateral border of the skin island, the SMAS was elevated 3 mm wider. After uncovering the nasal SMAS to

**Table 1 Case series summary**

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<tr>
<td>Nasal tip</td>
<td>5</td>
</tr>
<tr>
<td>Nasal supratip</td>
<td>4</td>
</tr>
<tr>
<td>Lateral nasal margin</td>
<td>4</td>
</tr>
<tr>
<td>Infraorbital area</td>
<td>4</td>
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<tr>
<td>Follow-up</td>
<td>6 mo–2 y</td>
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the adequate distance, the superior margin of the flap was incised at full-thickness and dorsal nasal arteries were ligated. After that, the SMAS was elevated together with the skin island by a precise dissection (► Fig. 2). For the reconstruction of the nasal tip and supratip, the lateral margin of the SMAS (extending along the lateral projection of the flap) was cut and the contralateral margin was cut as much as necessary to allow rotation, and then the flap was mobilized and transferred to the defect area (► Fig. 3). For the defects in the infra orbital areas, the nasal SMAS was cut from both the sides of the planned skin island up to the supratip area and the island skin flap was transferred. Flap donor areas were closed primarily (► Fig. 4).

**Results**

None of the patients developed flap necrosis. Although mild edema and venous insufficiency were observed in the flaps in the acute period only in the patients who underwent nasal tip reconstruction, these improved during follow-up. In the operated patients, no problem was observed in the donor area and nasal dorsal skin. No tumor recurrence was observed in the patients during the 6- to 24-month follow-up period. Aesthetic outcomes of the postoperative traces were good. The assessment of aesthetic outcome using VAS gave an average score of 7.1 indicating good aesthetics.

**Discussion**

Perinasal region defects occur because of oncologic, surgical, traumatic or iatrogenic reasons. The method of choice for the reconstruction of this region is determined considering the size and depth of defect and the aesthetic outcomes of final scarring.

Numerous methods are used for the reconstruction of the perinasal region. Secondary healing is preferred for the reconstruction of defects smaller than 5 mm in the medial canthus and alar groove; primary suturing or transposition flaps are preferred for defects smaller than 1 cm in the medial one-third aspect of the nasal dorsum, caudal dorsum, and sidewall; a bilobed flap is preferred for the reconstruction of defects between 0.5 and 1.5 cm in the nasal tip and sidewall; a V-Y advancement flap with subcutaneous pedicle is preferred for the reconstruction of defects smaller than 1.5 cm; and nasodorsal flaps are preferred for the reconstruction of defects smaller than 2 cm. forehead flaps, skin grafts, and free flaps can be used for larger defect areas. Reconstruction of the inferior one-third region of the nasal region using a SMAS flap together with skin graft has been described previously. In addition, reverse-flow SMAS has been used for the soft tissue support of the columnar region. However, to the best of our knowledge, there is no report in the literature on the nasal SMAS island skin flap. Increasing knowledge concerning the rich vascular configuration and nasal SMAS of

![Fig. 2](A) Preoperative view of the basal cell carcinoma on the nasal tip and planned flap. (B) Schematic view of the superficial arterial system of the patient external nose. (C) Nasal dorsal skin area in the inferior aspect of the flap was elevated in the subdermal plane. (D, E) Superficial musculoaponeurotic system was elevated together with the skin island and flap transferred. (F) Postoperative view 12 months after the operation.
Fig. 3 (A) Preoperative view of the basal cell carcinoma on the supratip. (B) Intraoperative view of the patient’s defect and planned flap. (C) Nasal dorsal skin area in the inferior aspect of the flap was elevated in the subdermal plane. (D, E) SMAS was elevated together with the skin island and flap transferred. (F) Postoperative view 12 months after the operation.

Fig. 4 (A) Preoperative view of the basal cell carcinoma on the left infraorbital area. (B, C) Intraoperative views of the patient’s lesion and planned flap. (D, E) SMAS was elevated together with the skin island and flap transferred. (F) Postoperative view 18 months after the operation.
this region indicates that this would be a reliable method in reconstruction.

Branches arising from the internal and external carotid systems in the nasal dorsum and their anastomoses make nasal SMAS a reliable pedicle in the dorsal aspect.\textsuperscript{17} Again, SMAS’s being thin and pliable in the dorsal aspect makes pedicle rotation and flap transfer easy. The pedicle’s being long allows flap transfer to the nasal dorsum, nasal tip, sidewall, and infra orbital areas.

Evaluation of arterial configurations via Doppler ultrasonography before surgery is not necessary in patients planning to undergo nasal SMAS island skin flap transfer. There is no need to use a loop at the reconstruction stage. The size of island skin flap can be planned to be $3.5 \times 2.5$ cm in the nasal radix. The relatively loose and excessive skin of the nasal radix allows primary closure of the donor site in the superoinferior direction and results in transverse scarring. Although it was not needed for our patients, the glabellar region can also be used for the closure of the donor site. The nasal radix is a mobile and pliable area and has good tissue and color match in perinasal reconstruction.

In this technique, contour irregularities or an unbalanced donor site could be expected to happen due to the rotated SMAS. However, there are not such issues in the flap donor area as shown in the photograph of patients, for the SMAS in the nasal dorsum is very thin and pliable. Moreover, the SMAS was widely allowed 3 mm more at the superior and both lateral than the edge of island skin area during surgery, so that the border of the island skin could prevent trap door deformity.

There are reports in the literature describing structural variations of the angular artery and lateral nasal artery in the arterial supply to the nasal dorsal area.\textsuperscript{11,18} However, in our method, these variations are not observed as the nasal SMAS is used. In the literature, a V-Y cutaneous flap of the nasal dorsum and axial-pattern cutaneous nasal dorsal flaps have been used for nasal-type defects.\textsuperscript{7,8} However, these flap applications are sophisticated surgeries and can be influenced by arterial variations. In such flaps, the isolation of the arteries is difficult and flap use is limited only to the nasal tip area. We think that the multidimensional use of the nasal SMAS–pedicled island skin flap together with a relatively easy reconstruction plan and surgical procedure would be effective in flap choice.

Forehead flap has good results with low rates of necrosis for the nasal reconstruction. However, there are some disadvantages. One of the major disadvantages is that the forehead flap is transferred in two or three stages. The other is the vertical forehead scar. If the patients have undergone surgery at the forehead region or the patients do not want to undergo forehead flap, the nasal SMAS-pedicled island skin flap is a good option.

Scarring and limited donor area are the major disadvantages of the nasal SMAS-pedicled island skin flap. As all study patients were elderly, scars in the surgical area healed with good aesthetic outcome. However, tight and young skin in young patients may unfavorably affect the final scar in the donor area and in other areas.

Financial Disclosure

The authors declare no competing financial interests.

References

Cranial Tip Suture in Nasal Tip Contouring

Milos Kovacevic, MD1 Jochen Wurm, MD2

1Praxis am Hanse-Viertel, Hamburg, Germany
2Department of Otolaryngology, Head and Neck Surgery, University Hospitals Erlangen, Germany


Abstract

The creation of both a functionally and aesthetically pleasing nasal tip contour is demanding and depends on various different parameters. Typically, procedures are performed with emphasis on narrowing the nasal tip structure. Excisional techniques alone inevitably lead to a reduction in skeletal support and are often prone to unpredictable deformities. But also long-term results of classical suture techniques have shown unfavorable outcomes. Particularly, pinching of the ala and a displacement of the caudal margin of the lateral crus below the cephalic margin belong to this category. A characteristic loss of structural continuity between the domes and the alar lobule and an undesirable shadowing occur. These effects lead to an unnatural appearance of the nasal tip and frequently to impaired nasal breathing. Stability and configuration of the alar cartilages alone do not allow for an adequate evaluation of the nasal tip contour. Rather a three-dimensional approach is required to describe all nasal tip structures. Especially, the rotational angle of the alar surface as well as the longitudinal axis of the lateral crus in relation to cranial septum should be considered in the three-dimensional analysis. Taking the various parameters into account, the authors present new aspects in nasal tip surgery which contribute to the creation of a functionally and aesthetically pleasing as well as durable nasal tip contour.

Keywords
► cranial tip suture
► alar surface septal angle
► nasal tip contour
► broad nasal tip
► pinched nose

One of the main aims in nasal surgery is to configure an enduring, functional, and aesthetically pleasing contour of the tip of the nose. Malformations, congenital deformities, weak cartilage, and surgical manipulations considerably affect the shape of the nasal tip. Apart from the aesthetic appearance, all these factors frequently affect the functional quality of nasal breathing.

Numerous different surgical techniques have been described to meet this challenge.1–11 These techniques are often associated with the excision of cartilage, incisions, sutures, or a combination of these. The removal of cartilaginous tissue inevitably leads to structural weakness of the supporting structures, which means that the results of these techniques are unpredictable and susceptible to uncontrollable deformity in the future. Suturing techniques are another way to narrow the nasal tip or improve its outline. Particularly, if the cartilage is weak, however, the most frequently used transdomal horizontal mattress suture may give rise to concavity immediately lateral to the dome and convexity in the lateral alar cartilage segments. In addition, this suturing technique is very often associated with inversion of the caudal margin of the lower lateral cartilage (LLC) and subsequent functional loss of cartilaginous support at the alar rim. Contractures from scar formation during wound healing frequently cause excessive narrowing of the nasal tip and deepening of the alar grooves, with unattractive inward buckling of the alae (a “pinched nose”). The harmonious balance of the individual nasal segments and the natural contours of the nasal tip itself are lost.

In his three-dimensional analysis, Toriumi described these typical postoperative changes in detail.12 According to his analysis, the alar rim buckles inward and a characteristic demarcation develops between the dome and the alar base. Concavity along the alar rim results in visual isolation of the
nasal tip and gives it an unnaturally rounded appearance. The aesthetically unfavorable shape of the nasal tip is pronounced, which means that it becomes more obviously noticeable. The inward displacement of the caudal margin of the low lateral cartilage further reinforces this negative effect.

Lateral crural strut grafts have been recommended to achieve a harmonious, continuous transition from the tip lobule to the alar lobule.\(^ {12,13} \) These grafts fixed on the undersurface of the lateral crura straighten and strengthen the lateral alar cartilages. In this way, the transition from the tip lobule to the alar lobule receives structural support, which prevents the typical unwanted depression of the alar rim and the development of an unnatural shadow. Furthermore, lateral crural strut grafts minimize the undesirable effects of transdomal mattress sutures.

Employing lateral crural strut grafts requires cartilage grafts, however, which are often not available, particularly for revision surgery. We now present a suturing technique for the configuration of a natural nasal tip contour: a technique that in many cases eliminates the need for additional cartilage grafts. The positioning and technique of the cranial tip suture (CTS) presented here everts the level of the caudal margin of the lateral crus, thus bringing it into alignment with the level of the cephalic margin. Our suturing technique provides structural support for the transition between the tip lobule and the alar lobule, an area that is so important for natural looking contours of the nasal tip, and thus gives an aesthetically pleasing result.

Patients and Methods

The retrospective study presented here includes 210 patients who, besides other corrective measures, had a CTS to improve the nasal tip contours as part of a primary aesthetic septorhinoplasty. The indication for CTS in all patients was their individual wish to reduce the size a nasal tip that was too wide or too bulbous. The patients did not have any marked asymmetry or malformations of the alar cartilage.

To ensure that we assessed the effects of the CTS method alone, patients who had cartilage grafts, in particular lateral crural struts and alar rim grafts, or other contouring sutures of the nasal tip were deliberately excluded from the study. The only further measure performed in the region of the nasal tip was an interfomal suture to readapt the domes to each other.

All procedures were performed between October 2010 and June 2014. The patients consisted of 168 women and 42 men aged between 18 and 61 years. The follow-up period was between 3 and 41 months. Clinical examinations and digital photographs recorded the overall contour of the nasal tip, the shape and stability of the alae, and the occurrence of complications or complaints.

Surgical Technique

An external approach was used in all patients, although the technique can also be used with an endonasal approach. After opening the nose and exposing the lateral crus and dome of the alar cartilage, only the excess of the cephalic part of the lateral crus that projects above the dorsal septum was reduced. This invariably leaves a strip of cartilage at least 10 mm wide in most cases: The strip maintained near the dome measured at least 5 to 6 mm.

The cranial and caudal tip points were then identified. For a CTS, the first entry point of the needle is approximately 3 mm below the dome and approximately 3 mm distant from the medial edge of the intermediate crus. The suture is then directed below the cartilage to the lateral crus. The needle exits approximately 1.5 to 2 mm behind the dome, likewise approximately 2 mm distant from the cephalic margin of the lateral crus. The decisive difference is in the return bite that now follows. In the classic transdomal suture, the return bite is taken parallel to the dome and therefore lies horizontally. In contrast, the return bite of the CTS is placed parallel to the cephalic margin of the lateral crus, approximately 2 mm behind the first exit point, and therefore lies vertically. The suture is once again passed beneath the cartilage to the intermediate crus. The exit point of the CTS is now at approximately the same level but approximately 2 mm medial to the initial entry point. A judicious choice of entry and exit points allows the suture to be tied with the knot positioned between the medial crus. A nonabsorbable 5–0 monofilament thread with a P3 needle has been shown to be best suitable (►Fig. 1A–C).

►Fig. 2 shows the principal effects achieved by the CTS. The caudal margin of the lateral crus rotates cephalically and approximates the same three-dimensional planes as the cephalic margin of the lateral crus. The position of the lateral crus surface subsequently changes in relation to the horizontal plane. In addition, the suture reduces the convexity of the crus. To make this clearer, ►Fig. 2 shows a possible unfavorable initial situation on the right side. The lateral crus surface here lies almost vertically to the horizontal plane. In this case, the two planes form an angle of almost 90 degrees. In direct comparison, the CTS on the left side causes the lateral crus surface to rotate cranially along its longitudinal axis. This opens the angle between the alar cartilage surface and the horizontal plane considerably. Ideally, the angle between the two planes should be between 135 and 165 degrees (►Fig. 3).

A more simple way of clinically determining the angle of rotation of the lateral crus is to look at the position of the alar cartilage surface in relation to the sagittal upper sepal margin. The resulting angle is called the “alar surface septal angle” (“ASSA,” ►Fig. 4). This angle should ideally be approximately 105 to 135 degrees. An angle greater than 155 degrees corresponds to a marked inversion of the caudal margin of the alar cartilage and is therefore unacceptable with respect to functional and aesthetic qualities.

The CTS has yet another beneficial effect. In addition to rotating the lateral crus surface, the cranial tip point is lowered whereas the caudal tip point is raised. This effect reinforces the configuration of an aesthetically pleasing supra-tip break. At the same time, the dome region itself is narrowed and any excess convexity of the lateral crus is reduced. The extremely important transition from the tip lobule to the alar lobule is structurally reinforced. Alar rim depression or retraction is prevented and a natural contour.
maintained. On the contrary, the typical undesirable concavity, found lateral to the dome, does not occur.

Fig. 5 shows the configuration of the right LLC after insertion of the CTS compared with the untreated left side. Note the considerable rotation of the lateral crus surface and the eversion of its caudal margin.

By altering the needle entry and exit points when placing the CTS, the effects of the suture can be modified to some extent. The deeper the needle enters the intermediate crus, the greater the rotational effect on the lateral crus surface. The more lateral to the dome the exit point on the lateral crus is placed, the greater the narrowing of the dome. It should therefore be ensured that the distance between the entry and exit points and the dome is not overall too great, as otherwise the risk of developing a lateral crus concavity increases. In the case of under or overcorrection, the suture can be removed at any time and a new one placed to meet the requirements. Once the CTS has achieved an adequate outward rotation of
the lateral crus, the new position of the cranial border of the lateral crus is secured by a second stitch. This positional fixation suture joins the lateral crus to the corresponding caudal end of the medial surface of the upper lateral cartilage or paraseptal tissue (Fig. 6). Polydioxanone (PDS) 5–0 thread with a P3 needle is recommended for this suture. It should in no way put the lateral crus under tension or move the lateral crus cephalically rather, it is intended to reinforce the rotational effect and prevent the cartilaginous structures from moving apart because of postoperative swelling and scar formation.

Results

Of the 210 patients, 193 (92%) had good or excellent postoperative results after the sole use of the suture technique presented here. All 193 cases had a harmonious and continuous transition from the tip lobule nasal to the alar lobule. Typical alar rim depression did not occur. No concavity developed along the lateral crus of the alar cartilage, nor was there any stenosis of the external nasal valve that impaired nasal breathing. Furthermore, there were no associated infections or suture fistulas, and in our patient population no alar rim retraction has been observed.

At the start of the study, PDS was used as the suture material for CTS in two patients. After initially promising results, there was a reduction in the immediate effects during the course of 4 to 6 months. The alar rim became progressively more depressed and the nose appeared slightly pinched. During the necessary revision surgery, it was found that the lateral crus was sufficiently stable but the surface was in an unfavorably steep position, at an angle of considerably more than 135 degrees. A new CTS was placed—this time with nonabsorbable suture material. The undesirable effects did not recur during follow-up. Intraoperatively, eight patients were found to have very thin, weak lateral crura. In these cases, too, the method was used in an attempt to rotate the lateral crus surface. The maximum rotation that could be achieved gave an ASSA of approximately 135 degrees. Further reduction of the angle in these patients would have caused concavity lateral to the dome because of the increased suture tension. Postoperatively, although there was no nasal pinching, there was still some unfavorable depression between the tip lobule and the alar lobule a few months later. Within 1 year, all eight patients had undergone successful revision surgery with alar rim grafts.

In four cases, the lateral crus was found to be in an extremely steep position, at an angle of considerably less than 25 degrees to the upper septal margin, that is, cephalic malposition. In these patients, an ASSA between 105 and 135 degrees could not be achieved without any additional measures. Transposition of the lateral crus was required after the vestibular skin had been released. Once an angle of approximately 40 degrees to the upper septal margin had been achieved, the CTS could be used to obtain the desired rotation of the lateral crus surface.

Case Reports

Example 1

Fig. 6A–C shows a patient with a long nasal hump, a slight axis tilt to the right, and an overhanging, moderately widened nasal tip. Fig. 6D–F shows the same patient 13 months after surgery for correction of the septum, nasal hump excision, medial, transverse and lateral osteotomies (low-to-low), a minimal cephalic trim, implantation of a columellar strut, and bilateral support spreader flaps, as well as bilateral CTS with positional fixation sutures to configure the nasal tip. To even out any minor irregularities, the dorsum was also lined with shaved cartilage paste.

A harmonious and continuous transition now extends from the tip lobule to the alar lobule. The nasal tip has been narrowed but there are no signs of pinching along the lateral crura.
Example 2
Before surgery, the patient shown in Fig. 7A–C had a pronounced cartilaginous/bony nasal hump. The nasal tip was slightly widened and clearly overhanging. Fig. 7D–F shows the results 12 months after the operation. The following procedures were performed: correction of the septum, nasal hump excision, medial and lateral osteotomies (low-to-high) on both sides, bilateral cephalic trims of approximately 3 mm, bilateral spreader grafts, a tongue-in-groove procedure, and CTS on both the sides.

Here, too, the transition between the dome region and alar base appears stable and harmonious, without any alar rim depression. The nasal tip has been narrowed, giving a pleasing aesthetic appearance, and there are no signs of a pinched nose.

Discussion
After rhinoplasty, many patients complain about a too bulbous or not sufficiently well-defined nasal tip. They find that the nasal tip is still too big, even though the configuration of the tip is in fact too narrow. The alar rim of these patients typically collapses and there is a clear demarcation between the tip lobule and the alar lobule. Not uncommonly, these patients also complain of impaired nasal breathing.12,14

A horizontal mattress suture is used for the classic transdomal suture, both to narrow the dome and to reduce excess convexity of the lateral crus.1,15 Nevertheless, experience with this technique has shown that, in many cases, undesirable effects occur during the course of wound healing and the formation of scar tissue. There is inversion of the lateral crus, displacing the level of the caudal margin below the level of the cephalic margin, with loss of cartilaginous structural support. In addition, concavity of the alar cartilage can often be seen immediately lateral to the dome.

Even by itself, the excision of cartilage from the cephalic margin of the lateral crus (cephalic trim) already has a significant effect on the relation between the newly created cephalic margin and the caudal margin. Excessive cephalic margin resection also leads to typical alar retraction, which gives the ala a notched appearance. In addition, there is often stenosis of the internal and external nasal valves with subsequent impairment of nasal breathing. These effects are even more marked in patients with cephalic malposition of the lateral crura, as the cartilaginous structural support along the alar rim is already weaker because of the position of the lateral crura alone. In this way, the techniques described contribute significantly to the typical undesirable effects on the contour of the nasal tip reported at the beginning.11,12,14,16,17

Fig. 6 (A–C) Preoperative pictures of a patient with a long nasal hump, a slight axis tilt to the right, and an overhanging, moderately widened nasal tip. (D–F) Results 13 months postoperatively after cranial tip suture and further procedures (please see the article for details).
Ideally, when contouring the nasal tip, every effort should therefore be made to obtain eversion of the caudal alar rim and a continuous transition from the tip lobule to the alar lobule. To achieve this goal, many techniques have been described in the literature. In particular, lateral crural strut grafts have been shown to be reliable even in the long term. These grafts support the lateral crus of the alar cartilage, usually along its entire length or even further, and can be used to contour the nasal tip for various indications.\textsuperscript{12,13} However, the technique is demanding and time consuming. It requires cartilage grafts, which are often needed for other purposes (or there may be an insufficient quantity in the nose itself). Lateral crural strut grafts may also give rise to palpable cartilage edges in the vestibule, which many patients find bothersome, and contribute to the nasal tip being unnaturally stiff. Another disadvantage is that an over-wide nasal base may occasionally be observed.

The potential complications of classic transdomal sutures have already been demonstrated in detail. For this reason, Guyuron and Behmand and Daniel recommend that the suture is placed as close as possible to the cephalic margin of the lateral crus.\textsuperscript{15,16} In our opinion, the desired effect of evertting the caudal margin is less pronounced than after the CTS.

Tebbets described the lateral crural spanning suture.\textsuperscript{4} This suture is tensioned between the two lateral crura and should in this way evert their caudal margin. It is a very powerful suturing technique, which should be used very precisely and requires a certain amount of experience, as too much tension in the thread may induce adverse effects such as alar retraction.

Dosanjh et al presented another interesting suturing technique.\textsuperscript{17} The so-called hemitransdomal suture is a simple interrupted stitch that grasps the cartilage a few millimeters above and below the dome. In each case, the entry and exit points are close to the medial margin of the intermediate crus or close to the cephalic margin of the lateral crus. The knot is placed between the medial crura. According to the authors, the hemitransdomal suture narrows only the cephalic half of the dome and at the same time leads to the desired eversion of the caudal margin of the lateral crus. Graphs and intraoperative photos in the article, however, show not inconsiderable pinching of the dome with the formation of a clear lateral crural concavity. Furthermore, we have the impression that there is less possibility of controlling the eversion angle.

To correlate the rotational angle of the lateral crus with the desired nasal tip contour, Çakır et al employed the lateral crural “resting angle.”\textsuperscript{18} This is the angle formed between the

![Fig. 7](image-url)
surface of the lateral crus and the upper lateral cartilage. According to the authors, this angle should ideally be approximately 100 degrees. A particularly obtuse 180 degrees angle correlates with the appearance of a pinched nose. However, in our opinion, measuring the angle between the upper lateral cartilage and the lateral crus does not allow a reliable assessment. The configuration of the upper lateral cartilage itself but also the use of spreader grafts or spreader flaps, for example, affects the position of the upper lateral cartilage in relation to the lateral crus surface—and hence the resting angle. The decisive rotation angle of the lateral crus surface however in fact remains unchanged. In other words, the method described by Çakir et al may give an apparently favorable angle of 100 degrees, even though the surface of the lateral crus is still in an unfavorable position. We therefore recommend that the rotation of the lateral crus surface is related to the unalterable horizontal plane or to the sagittal upper septal margin (ASSA). As already stated, the angle formed should optimally be 135 to 165 degrees or 105 to 135 degrees, respectively. In our experience, efforts should be made to achieve a larger angle with structurally weak cartilages compared with patients with stronger cartilages.

Critical assessment of the CTS, however, shows the limitations of the technique. Use of the CTS alone is not suitable for obtaining an aesthetic nasal tip contour in patients with cephalic malposition of the lateral crus. The unfavorably steep position of the lateral crura means that a CTS cannot provide adequate structural support for the caudal margin of the lateral crus. In such cases, transposition of the lateral crus is recommended. The CTS can then be successfully used as a supplementary measure in these patients.

In cases with very thin and weak cartilages, it is often impossible to achieve the desired rotation angle without simultaneously causing concavity of the lateral crus. There is therefore no reason to avoid structural cartilage grafts in these patients.

In addition, the use of nonabsorbable sutures is recommended for the CTS, as absorbable suture material apparently cannot resist the long-term shrinkage with scar formation.

**Conclusion**

The CTS has shown itself to be a simple and reliable technique for contouring the nasal tip. Eversion of the caudal margin and the caudal displacement of the lateral crus described produce a harmonious and continuous transition from the tip lobule to the alar lobule. In many cases, no additional cartilage grafts are needed. In our experience, the CTS can therefore be recommended as an appropriate amendment in the surgery of the nasal tip.

**References**

We read with interest the article by Soltani-Arabshahi and Tristani-Firouzi published in the *Facial Plastic Surgery* Journal in October 2013, on chemoprevention of nonmelanoma skin cancer (NMSC) in solid organ transplant patients (OTR). We commend them for their extensive review of the literature and thoughtful discussion on chemopreventive modalities from retinoids and nonsteroidal anti-inflammatory agents to photodynamic therapy and nutritional factors. As the population of long-term surviving OTRs increases, so does the need to prevent ultraviolet (UV)-induced NMSC, the leading form of cancer in this population. The least invasive preventive approach of sun avoidance via sunscreen use often gets missed in the management algorithm. In a November 2009 publication in the *British Journal of Dermatology*, Ulrich et al assessed the preventive effects of sunscreen use in chronically immunocompromised OTRs and found a marked difference in favor of the intent-to-treat sunscreen group. Regular use of sunscreens, as part of a consequent UV-protection strategy, significantly prevented the development of further actinic keratosis, invasive squamous cell carcinoma and, to a lesser degree, basal cell carcinoma in OTRs.

![Fig. 1 Wavelength spectrum coverage of common sunscreen ingredients.](image)

### Table 1 Modality for prevention of NMSC in solid organ transplant patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Level of support</th>
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<tr>
<td>Photoprotection</td>
<td>Effective</td>
</tr>
<tr>
<td>PDT</td>
<td>Effective</td>
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<tr>
<td>Imiquimod</td>
<td>Effective</td>
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<tr>
<td>Diclofenac sodium, topical</td>
<td>Potential prevention</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>Modest potential prevention</td>
</tr>
<tr>
<td>Oral retinoids</td>
<td>Effective for SCC</td>
</tr>
<tr>
<td>DFMO</td>
<td>Potential in BCC, no impact on SCC</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Consumption inversely associated with BCC, no impact on SCC</td>
</tr>
<tr>
<td>S-FU</td>
<td>Not studied in large randomized controlled trials</td>
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<tr>
<td>Ingenol mebutate</td>
<td>Not studied in immunosuppressed</td>
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<tr>
<td>Perillyl alcohol</td>
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<tr>
<td>Topical retinoids</td>
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<tr>
<td>Vitamin D</td>
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<tr>
<td>B-carotene</td>
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Abbreviations: S-FU, 5-fluorouracil; BCC, basal cell carcinoma; DFMO, difluoromethylornithine; NMSC, nonmelanoma skin cancer; PDT, photodynamic therapy; SCC, squamous cell carcinoma.
Soltani-Arabshahi and Tristani-Firouzi reported that “given the increasing number of patients on immuno-suppressive therapies who are at high risk of developing numerous and/or aggressive NMSC, the need for a safe and effective prevention strategy is rising.” We wholeheartedly agree and corroborate that further studies need to be performed to address chemoprevention options for areas with field cancerization. That said, due diligence should also be performed to encourage patients’ utilization of the least invasive, easily attainable, and cost-effective options such as broad spectrum sunscreens and ultraviolet protection factor clothing before progression to systemic chemoprevention treatments. Finally, sun-protective antioxidants (such as B-carotene supplementation and polypodium leucotomos extract) may have a role that has yet to be explored in this population. We present an evidence-based summary of the chemopreventive and noninvasive treatment options for NMSC treatment among OTRs (Table 1).
Bilateral Auricular Pseudocyst: Recognizing and Treating

Jonas Laschen, MD1  Frank R. Datema, MD, PhD2  Veronica C. M. Koot, MD, PhD3  Peter J. F. M. Lohuis, MD, PhD1

1 Department of Head and Neck Surgery and Oncology, The Netherlands Cancer Institute—Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands
2 Department of Otolaryngology/Head and Neck Surgery, Erasmus Medical Center, Rotterdam, The Netherlands
3 Department of Dermatology, Diakonessenhuis, Utrecht/Zeist/Doorn, The Netherlands


Address for correspondence Jonas Laschen, MD, Department of Head and Neck Surgery and Oncology, The Netherlands Cancer Institute—Antoni van Leeuwenhoek Hospital, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands (e-mail: j.laschen@nki.nl).

Auricular pseudocyst is characterized by an asymptomatic, benign cystic lesion of the auricular cartilage. When not recognized, it is a clinical presentation that can easily be misdiagnosed and subsequently be mistreated leading to unsatisfactory esthetical results or disease recurrence. A patient was presented with bilateral pseudocysts, which were surgically excised. The aim of the treatment of a pseudocyst is to have recurrence-free resolution and to restore the original auricular architecture while removing the cystic lesion. Three alternatives to surgery are described in the literature and all seem not to be sufficient. When the pseudocyst is treated at an early stage, surgical excision shows high success rates and preservation of the auricular architecture. According to the success rate described in the literature combined with the preservation of the auricular architecture, we recommend surgical excision for the management of auricular pseudocysts.

Case

The dermatologist presented us a 76-year-old woman with a bilateral, slowly progressive, and painful swelling of the upper auricle. There was no preceding trauma, insect bite, or inflammation. Physical examination showed a 1.5 cm skin-colored, fluctuant lesion on both the sides of the antihelix (► Fig. 1). The differential diagnosis included auricular pseudocyst, subperichondrial hematoma secondary to trauma, relapsing polychondritis, and traumatic perichondritis. Fine needle aspiration showed a viscous straw-yellow fluid. The diagnosis of an auricular pseudocyst was based on the typical clinical findings as described earlier, and on the macroscopical characteristics of aspirated fluid. Both the cysts were...
surgically excised under local anesthesia with the technique described later. Macroscopical examination revealed an intracartilaginous cyst devoid of epithelial lining, with sparse inflammatory cells (Fig. 2). Reactive changes of the cartilage were evident. The postoperative results were good with preservation of the auricular architecture. No recurrences were seen within 1-year follow-up period.

**Surgical Technique**

The surgical field was sterilized with chlorhexidine and prepared for surgery. The incision in the antihelical fold was precisely marked for aesthetical reasons. After local infiltration with lidocaine 2.0% and adrenaline 2.0%, the incision was made and the cyst was exposed (Fig. 3A). Then, a tangential incision of the lateral wall of the cyst (Fig. 3B).

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**Fig. 1** Patient with pseudocyst (arrow) of the right auricle.

**Fig. 2** Histological slide with hematoxylin and eosin staining. (A) Cyst filled with proteinaceous material. (B) Cartilage lining (no epithelium). (C) Chondrocyte.

**Fig. 3** (A) Incision of the antihelical fold (pseudocyst is exposed, arrow). (B) Tangential incision of the lateral wall of the cyst (lateral cartilage is marked, arrow).

**Fig. 4** (A) The lateral cartilaginous leaflet was resected and the borders were smoothened. (B) Flap was set back and the skin was closed with mattress sutures.
was made (►Fig. 3B). The lateral cartilaginous leaflet was resected—similar to the removal of the top of an eggshell—and the borders were smoothened (►Fig. 4A) to prevent secondary chondrodermatitis by pressure necrosis when sleeping. The skin flap was sutured back with a 4.0 Vicryl suture and additional 4.0 Vicryl mattress sutures were placed to prevent hematoma (►Fig. 4B).

**Discussion**

The etiology of the pseudocyst is unknown, but several hypotheses have been formulated. The dermatologist referred this patient with a bilateral, synchronously appearing auricular pseudocyst. The synchronous appearance suggests a congenital etiology of the disease. In this perspective, infection could give rise to a preexistent fragility in the intercartilaginous space of the auricle, which could lead to the formation of the pseudocyst. As shown in ►Fig. 2, the pseudocyst lacks epithelial lining demonstrative of the term “pseudocyst.” Moreover, it shows hyaline changes, characteristic for reactive changes. If these findings are combined with the fact that this entity is extremely rare, but very susceptible to trauma, we conclude that the auricular pseudocyst has a congenital origin. This is partially in line with the theory that chronic, low-grade trauma of the auricle, might induce the release of lyssosomal enzymes causing progressive dilatation and the formation of a cystic space.

The aim of the treatment of a pseudocyst is to have recurrence-free resolution and to restore the original auricular architecture while removing the cystic lesion. Three alternatives to surgery show up in the literature (see ►Table 1) with varying success.

Simple observation has been described as insufficient, because without treatment auricular pseudocysts are reported to cause further cartilaginous destruction, possibly resulting in cauliflower ear. However, Patigaroo et al advocate for an observation period of 3 months, because their study shows that pseudocysts do shrink with time and many recover completely.

Corticosteroid injections have been used with variable results. These intraleSION corticosteroid injections are administered with an interval of 3 weeks. Some studies, for example, the study of Bhandary and Mannil, find modest success in the treatment with corticosteroid injection. Of the 10 patients, 6 patients had recurrent pseudocysts and 3 suffered from thickening of the pinna. Especially, the risk of atrophy, deformities of the auricle, and the high chance of recurrence limit the use of this therapy. Thus, the overall consensus is that corticosteroid injections are not successful in the treatment of auricular pseudocysts.

A simple needle aspiration of fluid with tight pressure bandage is a more frequently applied alternative to surgery. Fluid is aspirated until the swelling disappears followed by compression with button bolsters for an average of 7 days. Aspiration alone almost always results in prompt reaccumulation of the pseudocyst with recurrence in all the cases. Compressing after aspiration has been suggested to decrease the amount of recurrences. There are no complications associated with this procedure, but because of the high-recurrence rate this therapy is not recommended as well.

The best treatment for the pseudocyst of the auricle is incision and drainage with removal of the anterior leaflet of the cartilage followed by pressure buttoning. This method is also called the deroofing procedure. Adjacent to the excellent results with respect to the recurrence-free course and the preservation of the auricular architecture, the deroofing procedure is associated with minor complications. In rare cases, perichondrial infection or hematoma can also be seen. We treated our patients with incision of the antihelical fold and excision of the lateral cartilaginous wall of the cyst. It is an easy procedure (►Figs. 3 and 4) and shows excellent results in long-term follow-up with preservation of the architecture of the auricle (►Fig. 5). When surgery is performed adequately, the risk of complications is low.

**Table 1** Different treatment modalities and recurrence rates (%)<sup>1–3</sup>

<table>
<thead>
<tr>
<th>Study</th>
<th>Simple aspiration</th>
<th>Corticosteroid injection</th>
<th>Surgical excision</th>
</tr>
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<tr>
<td>Patigaroo et al (n = 7)</td>
<td>85</td>
<td>43</td>
<td>0</td>
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<tr>
<td>Lim et al (n = 9)</td>
<td>100</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>Bhandary and Mannil (n = 10)</td>
<td>90</td>
<td>60</td>
<td>0</td>
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**Fig. 5** Follow-up 1-year postoperatively.
**Conclusion**

In summary, according to our experience and considering the success rate described in the literature combined with the preservation of the auricular architecture, we recommend surgical excision for the management of auricular pseudocysts. It is important to recognize and treat the pseudocyst at an early stage to avoid progression with cartilage destruction. When surgery is performed adequately, no recurrences or complications are seen.

**References**

Quality of Life in Patients Who Underwent Rhinoplasty

Ramin Zojaji, MD1 Mozhdeh Keshavarzmanesh, MD2 Hamid Reza Arshadi, MD3 Morteza Mazloum Farsi Baf, MD4 Sarvenaz Esmaeilzadeh, MD4

1 Department of Otohinolaryngology, Faculty of Medicine, Islamic Azad University, Mashhad Branch, Mashhad, Iran
2 Department of Otohinolaryngology, Mashhad, Iran
3 Department of Psychiatry, Faculty of Medicine, Islamic Azad University, Mashhad Branch, Mashhad, Iran
4 Faculty of Medicine, Islamic Azad University, Mashhad Branch, Mashhad, Iran

Address for correspondence Ramin Zojaji, MD, Arya Teaching Medical Hospital, ENT Dept., Islamic Azad University, Golestan 5, East Golestan Street, Jahanbany Street, Mashhad, Khorasan Razavi, Iran, postal code 9137714641 (e-mail: raminzojaji@yahoo.com).


ERRATUM

The publisher regrets two errors in the above article in Facial Plastic Surgery, Volume 30, Number 5, 2014, page 593 (DOI: 10.1055/s-0034-1396583). One of the author names under the article title was misspelled in the print and online versions. The name Sarvenaz Esmaeilzadeh should have read Sarvenaz Esmaeilzadeh. In the online version of this article on PubMed, the name Farsi Baf MM should actually read Mazloum Farsi Baf M.