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Avoiding and Treating DermalFiller Complications

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Avoiding and Treating Dermal Filler Complications

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Summary: All fillers are associated with the risk of both early and late complications. Early side effects such as swelling, redness, and bruising occur after intradermal or subdermal injections. The patient has to be aware of and accept these risks. Adverse events that last longer than 2 weeks can be attributable to technical shortcomings (e.g., too superficial an implantation of a long-lasting filler substance). Such adverse events can be treated with intradermal 5-fluorouracil, steroid injections, vascular lasers, or intense pulsed light, and later with dermabrasion or shaving. Late adverse events also include immunologic phenomena such as late-onset allergy and nonallergic foreign body granuloma. Both react well to intralesional steroid injections, which often have to be repeated to establish the right dose. Surgical excisions shall remain the last option and are indicated for hard lumps in the lips and visible hard nodules or hard granuloma in the subcutaneous fat. (*Plast. Reconstr. Surg.* 118 (Suppl.): 92S, 2006.)

The aesthetic benefit the patient achieves with temporary fillers is 90 percent technique and 10 percent substance. With permanent fillers, it's 99 percent technique.

Jean Carruthers¹

All injectable dermal fillers can cause complications. Late side effects can be divided into those caused by insufficient training or technical errors during injection and those caused by immunologic (allergic and nonallergic) reactions to the injected substance. In the case of late, nonallergic reactions, the pathologic substratum differs from injectable to injectable but can always be classified into one of three distinct forms of foreign body granuloma.² The histologic reaction is always similar,³ and the trigger for this sudden stimulation of macrophages might be a systemic infection of the patient.²

DERMAL FILLERS

Silicone, bovine collagen, Artecoll, and Restylane have been used worldwide.^{4,5} The first of these, medical grade fluid silicone of 350 centistokes (cS), was manufactured by Dow Corning, Inc., from 1954 to 1992, but banned by the U.S.

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Food and Drug Administration in 1967 for cosmetic use.⁶ A more viscous product, Silikon 1000, has been approved for retinal reattachment since 1998 and used off-label as a dermal filler. Bovine collagen (Zyderm, Zyplast) was introduced in 1981 and 1983 and became the standard for injectables. Artecoll has been distributed from 1994 to 2006, and Restylane started its triumphant advance in 1997. Since that time, a variety of fillers have been introduced, mainly to the European market. Radiesse is approved for facial bone augmentation and has been used off-label since 2003 for wrinkle treatment, and Sculptra is approved for facial human immunodeficiency virus lipodystrophy but has been used for wrinkle treatment since 2005. The U.S. Food and Drug Administration approved Restylane in 2003, Hylaform in 2004, Captique in 2005, and Juvederm in 2006 for the treatment of facial wrinkles.

For a complete list of the FDA status and approved uses for the fillers mentioned in this supplement, please see Table 1. As of this article's acceptance for publication in *Plastic and Reconstructive Surgery*, ArteFill, a product of Artes Medical, had not yet been approved by the FDA. For further information, please visit the following Web sites: www.plasticsurgery.org/news_room/press_releases/Injectables-at-a-Glance.cfm or www.surgery.org/press/news-release.php?iid=320§ion=news-botox.

The clinical persistence of an injectable and its effect on wrinkles depends on the amount, depth, and shape of the implant. A thin strand applied beneath a constantly moving wrinkle on a human face is absorbed faster than a round depot beneath the skin on a rat forehead or a human forearm. The carrier substance, whether quickly or slowly resorbable, may also play an important role in persistence. So far, only one of the implants—with the exception of silicone, polyacrylamide, and polymethylmethacrylate—is palpable longer than 9 months.^{7,8}

Although all filler substances, resorbable or nonresorbable, appear to be clinically and histologically safe, all may exhibit undesirable clinical side effects, and host defense mechanisms react differently to the various filler materials.¹ According to the histologic reaction that fillers stimulate, they have been classified as “volumateurs,” with little cellular invasion, and “stimulateurs,” with strong cellular reactions.⁹ Because the mechanism of late inflammation or granuloma formation is still unknown, early histologic findings are not useful in predicting possible late reactions to filler substances. Such late complications can be confirmed only by rigorous long-term clinical studies and by government-enforced reporting to a centralized independent implant registry.

To avoid or treat complications with dermal fillers, knowledge of their composition, physiologic tissue reactions, absorption time, and persistence is indispensable. Therefore, the fillers that are well-known and available worldwide are described below with respect to one or more of these characteristics.

Autologous Fat Grafts

- Liposculpture with the patient’s own fat.
- Preadipocytes (Fidia Advanced Biopolymers, Padua, Italy). No clinical data yet.
- Stem cells from adipose tissue (Cytori, Inc., San Diego, Calif.). No clinical data yet.

Autologous fat is rarely permanent, and its fate is unpredictable. There are convincing anecdotal cases published,¹⁰ but no statistics are available on fat graft survival. The key to long-term survival of injected fat (i.e., the development of functional preadipocyte or stem cell cultures) has yet to be discovered. Then, another question may arise: What happens to the surviving fat cells in the face, when patients get obese in later years?¹¹ Do they enlarge the same way the fat cells enlarge at locations from which they stem?

Bovine Collagen

- Zyderm I, Zyderm II, and Zyplast (Inamed Aesthetics, Santa Barbara, Calif.). U.S. Food and Drug Administration approved.
- Koken Atelocollagen (Koken, Tokyo, Japan).

Porcine Collagen

- Permacol (Tissue Science Labs., England).
- Fibroquel (Aspid, Mexico).
- Evolence (ColBar LifeScience, Herzliya, Israel). The company’s claim that Evolence lasts up to 1 to 2 years has still to be proven clinically.

Human Collagen

- Cosmoderm, Cosmoplast (Inamed Aesthetics). U.S. Food and Drug Administration approved.
- Isolagen (Isolagen Technologies, Houston, Texas). Collagen from the patient’s own cultured fibroblasts; in clinical trials.
- Fascian (Fascia Biosystems, Beverly Hills, Calif.). Strips from human fascia; U.S. Food and Drug Administration approved.
- Cymetra (LifeCell Corporation, Branchburg, N.J.). Injectable microparticles from human skin; U.S. Food and Drug Administration approved.

So far, all collagen preparations disappear clinically within 4 to 6 months and are histologically absorbed between 3 and 9 months, depending on the volume injected.⁸ Cultured autologous fibroblasts (Isolagen) have yet to demonstrate their survival and effectiveness.

Hyaluronic Acid Gels

- Restylane (U.S. Food and Drug Administration approved), Perlane, Fineline, SubQ, Macrolane (Q-Med, Uppsala, Sweden; and Medicis Aesthetics, Scottsdale, Ariz.) derived from *Streptococcus equi*.
- Hylaform (Inamed Aesthetics); from rooster combs; Hylaform Plus, Hylaform Fineline, all U.S. Food and Drug Administration approved.
- Juvederm 18, 24, and 30 (Leaderm, Paris; and Inamed Aesthetics). From *Streptococcus equi*; U.S. Food and Drug Administration approval pending.
- Captique (Inamed Aesthetics; and Genzyme, Boston, Mass.); U.S. Food and Drug Administration approved.

- Rofilan Hylan Gel (Rofil Medical International, Breda, The Netherlands).
- AcHyal (Tedec-Meiji Farma, Spain).
- Matridur (BioPolymer, Siershahn, Germany).
- Hyal-System (Merz Pharma, Frankfurt, Germany); for two-dimensional augmentation.
- Puragen (Mentor Corp., Santa Barbara, Calif.); contains lidocaine.

Natural fillers such as collagen and hyaluronic acids are broken down by enzymes, absorbed, or phagocytized slowly, with minimal histologic reaction. After further purification of Restylane in 1999, its incidence of complications has been markedly reduced.

Polymethylmethacrylate Microspheres

- Artecoll (Rofil Medical International) consists of microspheres 30 to 42 μm in diameter, suspended in bovine collagen.
- ArteFill (Artes Medical, San Diego, Calif.) consists of microspheres 30 to 50 μm in diameter but more highly purified than those in Artecoll; the microspheres are suspended in bovine collagen manufactured in the United States.
- Aphrodite Gold (European Medical Contract Manufacturer, Nijmegen, The Netherlands) is the former Artecoll in a new package, distributed outside Europe and the United States.
- Metacrill (Nutricel Laboratorios, Rio de Janeiro, Brazil); polymethylmethacrylate microspheres 1 to 80 μm in diameter, with impurities similar to those of the former Arteplast, suspended in carboxygluconate gel.
- Bioplasty (Dr. Almir Nacul, Porto Alegre, Brazil) is similar to Metacrill.
- Precise (Clinica Estetica, Tijuana, Mexico) is similar to Metacrill.

Polymethylmethacrylate microspheres remain unchanged throughout the patient's life but are encapsulated individually with connective tissue, macrophages, and sporadic giant cells. They provide scaffolds for continuously renewed connective tissue formation and vascularity and therefore are considered "living" implants.¹²

Silicone Fluids

- Silikon 1000 (Alcon Laboratories, Fort Worth, Texas) has been U.S. Food and Drug Administration approved for retinal reattachment since 1998.
- SilSkin, 1000 cS (Richard-James Development Corp., Peabody, Mass.) is in clinical trials for

facial wrinkles but is not U.S. Food and Drug Administration approved.

- PMS 350 (Vikomed, Germany) is fluid silicone of low viscosity (350 cS) similar to the former Silicone 360 from Dow Corning.

Slowly resorbable fluid fillers such as fluid silicone^{4,6,13} and polyacrylamides dissipate into the tissue, are clinically inconspicuous, and cause little fibrosis. Large volumes, however, can dislocate in patients with loose connective tissue through muscle movement and gravity. They are considered "inert implants."¹²

Polyacrylamide Gels

- Aquamid (Ferrosan AS, Copenhagen, Denmark) polyacrylamide gel 2.5% in water.
- Interfall (Interfall Ltd., Kiev, Ukraine).
- Bio-Alcamid (Polymekon, Milan, Italy); 4% polyacrylamide cross-linked with polyalkylimide.
- Outline (ProCytech, Bordeaux, France) is temporary and absorbed within 1 to 2 years.
- Amazing Gel (FuHua Ltd., ShenZhen, China).
- Formacryl (Bioform, Moscow, Russia).
- Argiform (Bioform) with silver ions as an antibiotic.

Polyacrylamide gels are well tolerated¹⁴ and slowly absorbed by the body over many years. They either dissipate (Aquamid) like fluid silicone or are kept in place (Bio-Alcamid) by means of a fibrous capsule (endoprosthesis). The effect of polyacrylamide gels on wrinkles has not undergone sufficient clinical and scientific testing. Like silicone, polyacrylamide causes a rather high incidence of late complications if injected in large quantities.²

Other Injectables

- Radiesse (Bioform, Inc., San Matteo, Calif.) is composed of calcium hydroxylapatite (constituent of bone and teeth) microspheres of 40 μm suspended in carboxymethylcellulose gel. When the cellulose is absorbed, the calcium microspheres often appear white beneath the vermilion or thin skin. It is a safe injectable and induces almost no foreign body reaction but is absorbed at 9 to 12 months.⁸
- Dermalive and Dermadeep (Dermatech, Paris) are composed of hydroxyethyl methacrylate particles suspended in hyaluronic acid. Hydroxyethyl methacrylate particles are packed after injection and absorbed and phagocytized

within 1 to 2 years.⁸ They cause the highest rate of granulomas¹ and should be used epiperios- teally only.

- New-Fill and Sculptra (Sanofi-Aventis, Stras- bourg; and Dermik Aesthetics, Berwyn, Pa.) consist of microspheres from polylactic acid (1 to 50 μm) suspended in methylcellulose. New-Fill and Sculptra appear to be safe and effective in larger quantities in facial defects such as facial lipodystrophy or chin and malar aug- mentation. The microspheres induce an in- flammatory response and foreign body reac- tion and clinically disappear beneath wrinkles at 6 to 9 months.⁸ Their “skin-thickening ef- fect” after injections into the residual subcuta- neous fat in human immunodeficiency virus patients with facial lipodystrophy is not yet un- derstood.
- Matridex (BioPolymer, Siershahn, Germany) consists of dextran beads of 40 μm suspended in hyaluronic acid (after U.S. Food and Drug Administration approval, it will be distributed in the U.S. by AART, Reno, Nev.).
- Reviderm intra (Rofil Medical International) consists of dextran beads 40 μm in diameter suspended in hyaluronic acid. Dextran micro- spheres induce a pronounced foreign body reaction and disappear within 6 to 9 months.⁸
- Evolution (ProCytech Labs., Bordeaux, France) consists of polyvinyl microspheres sus- pended in a rather fast absorbable polyacryl- amide gel. The microspheres are well tolerated and permanent, whereas the gel diminishes clinically and histologically over 9 months.⁸
- Bion-Blue (Polymekon, Milan, Italy) is an 8% polyvinyl-alcohol gel that is absorbed quickly (Table 1).

AVOIDANCE OF COMPLICATIONS

Patients who are contemplating a wrinkle treatment for the first time and are not sure about their choice should try collagen or hyaluronic

acid. No hyaluronic acid, including Restylane or Juvederm, has demonstrated a significantly longer duration than Zyderm or Zyplast; all of these fillers last for approximately 4 to 6 months.⁸ If the pa- tients are satisfied but do not want to repeat the treatment every 6 months, they should consider a longer lasting injectable such as Sculptra or Radiesse or a permanent injectable such as sili- cone or ArteFill.

Physicians may reduce the risk of complica- tions by selecting appropriate patients and by us- ing proper injection technique. With regard to the first of these issues, there are anecdotal reports of patients with a tendency for keloid or hypertro- phic scar formation who developed granulomas in both of the sites that were injected with dermal fillers.

There are also reports of patients with sarcoid- osis who developed a similar histologic picture at their injection sites. Because of these small num- bers, a relationship between hypertrophic scarring or sarcoidosis and susceptibility to foreign body granuloma cannot be established at this time.

Considerations

Thin Skin

In general, thin skin, 0.4 mm thick, as in the lids, is a contraindication for all fillers, especially around the eyes and in cheeks that have many tiny wrinkles. At such sites, laser resurfacing or a chem- ical peel is the treatment of choice.

Temporary Treatment of Lips before a Permanent Filler

Prior injections of collagen can cause scar for- mation beneath the vermilion border, which may lead to unevenness or asymmetries when a per- manent filler is injected. These fine lumps and bumps can easily be corrected, preferably 3 months later, if the patient does not object to waiting during this period.

Table 1. Classification of U.S. Food and Drug Administration–Approved Injectables

Brand Name	Active Ingredient	Mechanism of Action	Biodegradable	Persistence in Tissue
Zyderm	Collagen	Volumizer	Yes	4 mo
Restylane	Hyaluronic acid	Volumizer	Yes	6 mo
ArteFill*	PMMA	Stimulator	No	Permanent
Silikon 1000	Silicone	Volumizer	No	Permanent
Radiesse	Calcium apatite	Volumizer	Yes	1 yr
Sculptra	PLLA	Stimulator	Yes	1 yr
Autologous fat	Living fat	Volumizer	Yes/no	Unpredictable

PMMA, polymethylmethacrylate; PLLA, poly-L-lactic acid.

*As the time of this article’s acceptance for publication in *Plastic and Reconstructive Surgery*, ArteFill, a product of Artes Medical, had not yet been approved by the U.S. Food and Drug Administration.

Laser Treatment after Dermal Fillers

Most lasers cause a burn injury of the superficial dermis, which forces it to contract. All longer lasting implants lie subdermally and are not affected by the laser rays or its induction of high temperature. Lasers exert heat well below the approximate melting point of silicone (600°C) and polymethylmethacrylate (125°C). Deep wrinkles, which will withstand laser treatment, can even be injected with a longer lasting filler directly before laser therapy; the concomitant swelling facilitates the effect of the laser.

Permanent Makeup on Top of Injectables

Permanent makeup is delivered to the upper papillary dermis, whereas particulate fillers are delivered to the junction between the dermis and the subdermis, so there is no interference between these two agents. A mature ArteFill implant, for example, behaves like a scar; it is a living tissue that can be tattooed, lasered, dermabraded, or peeled. Like a scar but unlike pure fillers (“volumizers”), an ArteFill implant heals by itself.⁹

Temporary Filler on Top of a Permanent Filler

So far, there has been no report of any patient who had an untoward reaction to a second filler implanted over any other filler. Fear of inducing granuloma formation is hypothetical at this time.

Temporary Filler Preceding a Permanent Filler

In Europe, thousands of patients have received semipermanent or permanent fillers after temporary fillers, and no interference between the two has been reported thus far.

Visibility of Permanent Implant as Patients Age

Although the thickness of the skin at the extremities decreases in old age, the facial skin thickens with age.¹⁵ Therefore, permanent implants beneath the nasolabial folds will not become visible, even in patients in their 90s.

Touch-Up Injection

Most patients will require one to three touch-up injections. They should be performed 1 to 3 months after the first implantation if there is no reason (e.g., unevenness, asymmetry) to do it earlier. After 3 months, a permanent implant has assumed its final shape, and the wrinkle above it has been restored to the thickness of the surrounding skin.

Weather Conditions

Two patients developed longer lasting swelling of their injected lips after driving a snowmobile all day in northern Canada. Therefore, the lower face should be covered during cold weather sports such as skiing or mountain climbing and during any other exposure to extreme cold.

Questionable Contraindications

Autoimmune Diseases and Collagen

In the early 1990s, some physicians and lawyers claimed a correlation between collagen injections and subsequent polymyositis and dermatomyositis in some patients. The U.S. Food and Drug Administration took this possibility very seriously but decided in 1995 that “a causal relationship between collagen injections and PM/DM or other connective tissue diseases listed, has not been established.”

Compatibility of Different Fillers

Several physicians have injected Restylane (or other collagen or hyaluronic acid fillers) intradermally, directly on top of the subdermal implant of a longer lasting filler in the same session for treating glabellar frown lines, without any reported adverse events.

Diabetes

Because wound healing is normal in these patients, except for neurologic foot ulcers, diabetes is not a contraindication to any filler.

Human Immunodeficiency Virus Patients

The microspheres in some products, such as ArteFill, stimulate simple granulation (scar tissue) formation similar to that associated with surgical or traumatic wounds. Immune deficiency and highly active antiretroviral therapy are not contraindications.

Immunodepressed Patients

In general, wound healing is not delayed in these patients, because fibroblasts need an approximately 10-fold higher concentration of immunosuppressive therapy to be affected than do immunocytes. Therefore, immune depression is not necessarily a contraindication to any type of filler.

Lupus

Systemic lupus is an autoimmune disease characterized by anti-DNA antibodies. The U.S. Food and Drug Administration has dismissed any cor-

relation of collagen injections with autoimmune diseases. So far, systemic lupus is not a contraindication for dermal fillers.

Rheumatoid Disease and Fillers

Particles and microspheres stimulate granulation (scar tissue) formation, as in surgical or traumatic wounds. Theoretically, collagen synthesis could be overstimulated, but this does not occur in patients with rheumatoid diseases. If wound healing is normal, rheumatoid disease is not a contraindication for dermal fillers.

Scleroderma

Because wound healing is normal in scleroderma patients, dermal fillers are not a contraindication.

Sebaceous Skin

Thick, oily skin is associated with fewer and later wrinkles. Patients with such skin are ideal candidates for two to three sessions of particulate fillers. However, during implantation, deep pores may be inadvertently hit, possibly causing a subsequent leak or pustule of the filler.

Skin Types

In general, a lighter skin is more prone to allergic reactions than a darker complexion. Problems with fillers, however, have only occurred in patients with extremely thin skin, where even sub-

dermal injections can end up close to the epidermis.

Correct Injection Technique

Acne Scars and Long-Lasting Fillers

This is the only case in which particulate materials must be injected very superficially; one has to see the gray of the needle under the skin, and blanching should occur. If this lasts for more than a few minutes, the implant should be spread and dispersed with one's fingernail.

Dark Shadowed Eyelids

The orbital rim has to be augmented strictly epiperiosteally with any filler by scratching the needle tip on the bone. Care has to be taken to not hit the orbicularis muscle because of subsequent nodule formation.

Gray of the Needle

The gray of the needle should never (except in acne scars) be visible through the skin; if it is, placement is too superficial (i.e., intradermal). The shape of the needle should always be apparent, indicating correct subdermal placement (Fig. 1).

Intradermal Injection of Long-Lasting Fillers

The only indications for superficial injections are acne or surgical/traumatic scars, which are not mobile like wrinkles. When treating these scars,

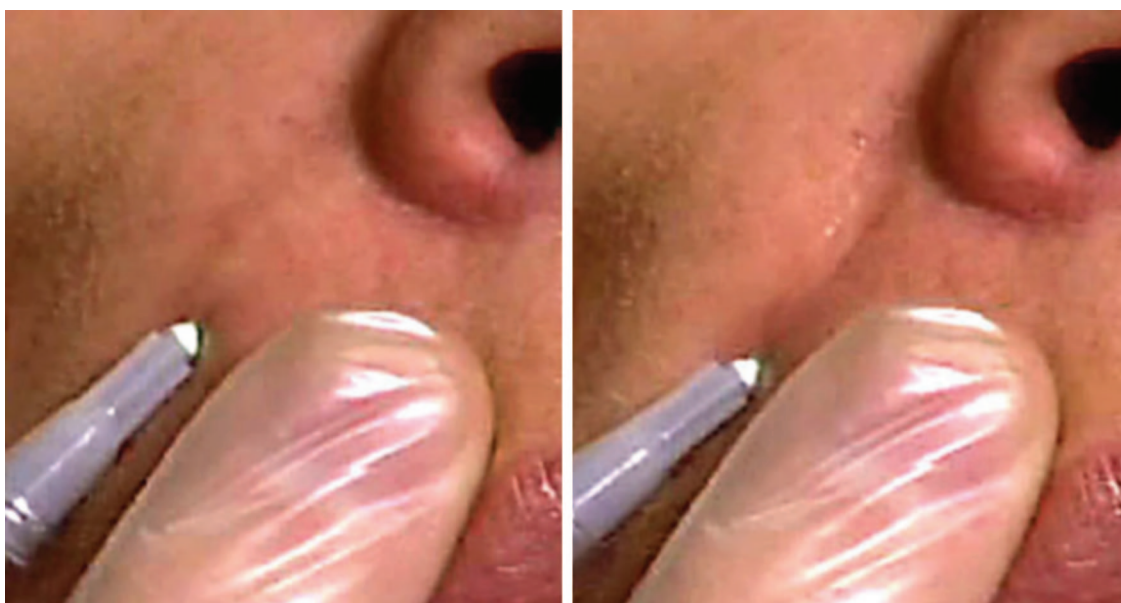


Fig. 1. The correct subdermal injection. If properly inserted, one can pull down the dermis with the needle into the fat.

there is little danger of superficial granules, which can occur, for example, in nasolabial folds, deep forehead furrows, or horizontal neck folds.

Intramuscular Injection of Any Filler

This is absolutely contraindicated because the muscle dislocates any implant to uncontrolled sites and forms lumps (similar to the way the muscle of a shell forms a pearl).

Lip Augmentation

Most side effects after lip augmentation occur in the 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 type of filler, because they can be compressed into lumps. Instead, one should inject 30 to 50 tiny submucosal microdroplets along the dry-wet border (Fig. 2).

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 infra-orbital block) is the injection of the local anesthetic into the labiogingival fold.¹⁶

Microdroplet Technique for Wrinkles

Fluid injectables such as collagen, hyaluronic acids, or silicone dissipate into the surrounding dermis; therefore, overcorrection with these

agents in the form of little intradermal blebs is permissible. Particulate fillers, in contrast, remain in the bleb or tunnel where they are injected.

Postinjection Care

There is no way to prevent the “physiologic” swelling after injection, which allows macrophages and fibroblasts to invade the implant and encapsulate the particles or microspheres. Cold gel compresses may be comfortable, but there is no proof that they prevent swelling or bruising. Reducing facial muscle movement as much as possible during the first 4 days may prevent clumping (Fig. 3).

Needle Showing through Skin

Except during injections of collagen and hyaluronic acid for fine lines, the gray of the needle should never be visible through the skin; if it is, placement is too superficial (e.g., intradermal). However, the shape of the needle should always be apparent, indicating correct subdermal placement (Fig. 1).

Subdermal Implantation

The thickness of the facial dermis varies from 0.2 mm in the lids to 1.0 mm in the glabellar region, and is diminished to approximately one-quarter of this in a wrinkle. The outer diameter of a 26-gauge needle is 0.45 mm. Therefore, all viscous and particulate injectable implants should be placed in the superficial subdermic (i.e., dermal-subdermal junction) (Fig. 1).^{7,12} An exception is acne scars.



Fig. 2. Augmentation of the vermillion border (white roll) is safe and easy because of a natural “pocket” underneath. Submucosal injection of strands may lead to lumps. Therefore, the microdroplet technique is recommended.



Fig. 3. If blanching occurs during injection of a long-lasting filler, one should stop immediately and try to disperse the filler downward and sideways with pressure from the thumbnail.

Superficial Implantation

If blanching is seen with longer lasting substances during injection (Fig. 4), the needle has to be withdrawn, the injected substance dispersed with the fingernail, and the needle inserted one needle diameter deeper. Later, little granules can occur, which can easily be leveled and erased by dermabrasion or shaving.

Massaging the Implant

There is no rationale for massaging the implant, which may flatten and disperse it and cause swelling and bruising. All particulate implants are meant to be a support structure (flexible splint) beneath the wrinkle, preventing it from further deepening. As these supports allow the dermis to recover its former thickness, the wrinkle disappears. Thus, these support structures should not be broken or dispersed with massaging. An exception may be microdroplets of fluids and Sculptra. One still has to keep in mind that the spaces in the fibrillar network of the dermis are 10 μm or less.



Fig. 4. One droplet of Kenalog is injected intradermally into a tiny wrinkle. It causes “blanching” for a few minutes.

“Poker Face”

Early facial muscle movement during eating, speaking, smiling, and smoking may push the implanted strands a 0.1 mm deeper into the dermal fat—and the wrinkle repair may be compromised. Facial expressions should be kept at a minimum during the first 3 days.

EARLY COMPLICATIONS

Attributable to Technique (Table 2)

Asymmetry after Implantation

The swelling that occurs with implantation can interfere with clinical judgment and can be the reason for unevenness in the lips and elsewhere. Correction is best performed 1 to 3 months later if no other reason applies.

Blanching after Injection

This occurs directly after implantation of any filler material when it is injected too superficially (Fig. 4). In acne scars, however, blanching is required for correct implantation and will disappear within 5 to 10 minutes. In all wrinkles and folds, blanching should be eliminated by firm smoothing motions with the fingernail (Fig. 3) to force it downward and sideways. Otherwise, persistent superficial granules may result.

Blindness after Injectables

This has been described for all types of injectables, from autologous fat, to anesthetics in the nose and around the eye, to collagen injections

Table 2. Classification of Dermal Filler Complications*

Early side effects
Erythema, redness
Edema, swelling
Ecchymosis, bruising
Pain, discoloration
Undercorrection or overcorrection
Skin necrosis, infection
Embolism (blindness)
Cold sore after lip injection
Late complications
Chronic inflammation
Late allergic reaction
Nodules, elevations
Asymmetry, distortion
Dislocation, migration
Hypertrophic scarring
Telangiectasia
Filler-related complications
Granuloma, “sterile abscess”
Lipoatrophy after injectables

*Data from Hexsel, D. M., Hexsel, C. L., and Iyengar, V. Liquid injectable silicone: History, mechanism of action, indications, technique, and complications. *Semin. Cutan. Med. Surg.* 22: 107, 2003.

into the glabella.^{17,18} Blindness occurs extremely rarely and is caused by injection into the supratrochlear artery, which is connected to the ophthalmic artery; however, it occurs only if one injects through a resting needle. In contrast, the needle through which viscous or particulate fillers are delivered has to be constantly moved back and forth during injection because of the high viscosity of the gel.

Difference between Lumps or Nodules and Granuloma

Lumps appear immediately within the first 4 weeks; mostly, they are single, well confined, located in the lips, and do not grow.² True granuloma appears late (mostly after 6 to 24 months) at all injected sites approximately at the same time; they grow rather fast and react well to intralesional steroid injections.²

Disappearance of Permanent Implants

Larger particles or microspheres can neither disintegrate quickly nor migrate. If there is no cosmetic effect after injection, the implant must have been injected too deeply (e.g., into the subcutaneous fat) or early facial muscle movement has pushed the implanted substance into the subcutaneous fat. Early muscle movement can be diminished by using a transparent tape (Fig. 5) that reminds the patient not to smile for 3 days.



Fig. 5. A transparent bandage will remind the patient to control smiling during the first few days after injection beneath the nasolabial fold.

Granules after Superficial Implantation

These can occur after too superficial (i.e., intradermal) implantation and can cause a real ridge (Fig. 6), which must be leveled and erased by dermabrasion or by surgical shaving (as in taking a skin graft). This area will heal without scarring.

Lumps in the Lips

These are formed by the movement of the lip muscles during the first week after injection, when the implant is still a paste. Injected strands are compressed into pearls (Fig. 7, *above*). At 4 weeks after implantation of Sculptra or ArteFill, when tissue ingrowth is at its maximum, the size of the lumps can be reduced to approximately half with intralesional Kenalog injections. Because lumps of Radiesse or Dermalive show little tissue ingrowth, steroids are not effective, so they have to be excised (Fig. 7, *below*).¹⁹ Lumps in the lips can be prevented by the microdroplet injection technique (Fig. 2).

Lumps Inside of the Oral Commissure

These can occur when the filler has been implanted into the orbicularis muscle. If they are disturbing to the patient, they can be reduced with Kenalog or removed through a transmucosal stab incision.

Lumps in the Marionette Line or Nasolabial Fold

If they derive from a particulate filler, they can be diminished with steroid injections (Figs. 4 and 8); if the source is a fluid injectable, sometimes lumps can be punctured in an early stage.

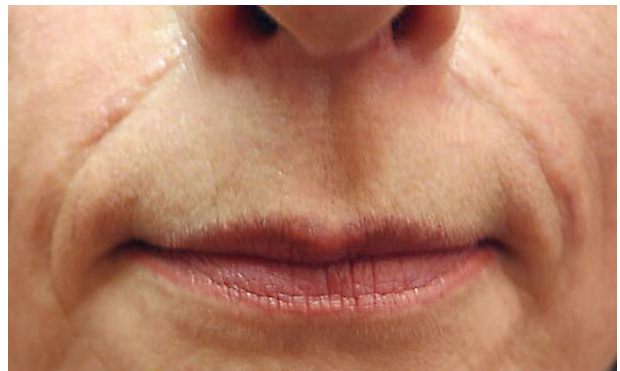


Fig. 6. Ridges in both nasolabial folds after too superficial an injection of Arteplast. These ridges can easily be leveled by dermabrasion or shaving.



Fig. 7. (Above) Small lumps in the lip after injection of Radiesse into the body of the lip. (Below) Careful excision of the lumps will leave no scars behind.



Fig. 8. Prominent ridges instead of frown lines after intradermal injection of silicone fluid. Interlesional steroid injections could permanently diminish it by half.

Redness after Implantation

This is often caused by implantation that is too superficial (i.e., intradermal) (Fig. 9). Redness can be reduced by intense pulsed light, intralesional Kenalog injections (Fig. 3), and in later stages by dermabrasion.



Fig. 9. The necessarily "intradermal" injection of silicone into acne scars led in this patient to acute inflammatory nodules. Intralesional injections of Kenalog plus 5-fluorouracil in a 1:3 ratio solved the problem within 2 weeks

Skin Necrosis after Injectables

This complication has been described for Zylplast and other fillers that have been implanted subdermally through a resting needle and whose injection inadvertently blocked a subdermal artery. In contrast, particulate fillers cannot be injected through a resting needle. Because of their high viscosity, the needle has to be moved constantly forward and backward during delivery of the strands. This is consistent with the fact that, so far, no cases of forehead skin necrosis have been reported for longer lasting fillers.

Swelling after Injection

The swelling that occurs during implantation can cause difficulties in judging the right amount of injectable and therefore cause unevenness in the lips and elsewhere. Correction is best performed 3 months later if no other reasons apply.

Attributable to the Implant (Table 3)

Acne after Filler Injections

There is no causal relationship between acne and treatment with any filler. If the filler is injected too superficially into the papillary dermis, it can be extruded through sebaceous glands or it will look like a pimple, which has to be pressed out. In contrast, chronic swelling and redness is rather frequent in the early postimplantation period.

Allergic Shock to Any Filler

This is a theoretical possibility with most fillers, which may sensitize the patient. One case was reported in Italy in 1997, where a patient in a doctor's office developed allergic shock after the eighth in-

Table 3. Potential Complications after Dermal Fillers

Filler	Early Technical Complications	Possible Late Adverse Events
Zyderm/Zyplast	Redness, ridges, nodules, embolism, ¹⁷ glabellar skin necrosis, acute allergy	Late allergy, cystic granuloma (sterile abscess, chronic inflammation) ²
Restylane and other HA fillers	Redness, ridges, nodules, acute allergy	Late allergy, cystic granuloma (sterile abscess, chronic inflammation), ² lipoatrophy ²⁰
ArteFill	Redness, ridges, nodules, acute allergy,	Nodules, chronic inflammation, sclerosing granuloma ²
Silikon 1000	Redness, ridges, nodules	Chronic inflammation, dislocation, edematous or cystic granuloma ²
Radiesse	Redness, nodules, ¹⁹ ridges,	Chronic inflammation, rare granuloma
Sculptra	Redness, ridges, nodules, lumpiness,	Nodules, sclerosing granuloma, ² lipoatrophy ²⁰
Aquamid Bio-Alcamid	Redness, ridges, nodules, infection	Infection, dislocation, cystic or sclerosing granuloma ²
Dermalive	Redness, ridges, nodules, hypertrophic scarring,	Chronic inflammation, frequent sclerosing granuloma ²
Autologous fat	Absorption, fat cysts, ¹⁰ embolism	Volume increase during later obesity ²¹¹

HA, hyaluronic acid.

jection of Artecoll.¹² Systemic treatment with 1000 mg of prednisone per infusion resolved the problem within hours. Unfortunately, double allergy testing in advance does not prevent this rare event.

Allergy to Bovine Collagen and Hyaluronic Acids

This may occur in approximately 3 percent of patients injected with bovine collagen and in an estimated 0.1 percent of patients injected with hyaluronic acids or ArteFill (Fig. 10).¹² In the skin test, an acute antibody reaction to the bovine collagen or hyaluronic acid is seen as a hot, red, swollen, coin-sized spot, often developing within 30 minutes. In the face, the swelling, redness, and heat may start overnight and last for 3 to 7 days if not treated immediately with systemic cortisone tablets or injections (Figs. 10 and 11).

A rare variant of collagen hypersensitivity is the late type IV allergy caused by immune cells after 1 to 6 months. This is characterized by hardening, itching, and redness at the implanted sites. The lesions must be treated like granulomas, with intralesional steroids.²

Capillaries at the Injection Site

Dilated venous capillaries are a sign of hyperactivity within the implant and may cause a bluish coloration of the injection site. They can develop after intradermal injections of any filler and are easily treated with several sessions of intense pulsed light.

Cold Sore after Lip Augmentation

Every third person suffers from oral herpes simplex infections of the lips. In these patients, the virus



Fig. 10. (Above) A rare case of acute allergy 2 days after injection of 1 cc of Artecoll and 2 months after a negative skin test. (Below) Resolution 2 days later after intralesional Diprosone and oral Celestamine.

can be activated by the implantation of any filler. Patients with a history of prior infections should be pre-treated with Valtrex or acyclovir. The best treatment is early evacuation of the blisters with scissors and/or immediate treatment with acyclovir ointment.



Fig. 11. (Left) Acute allergic swelling of both cheeks 4 days after injection of hyaluronic acid in both tear trough deformities. (Right) Recovered 2 days after administration of Celestamine and antihistamines.



Fig. 12. Hypertrophic scarring in both nasolabial folds after wrongful intradermal injection of Dermalive. Intralesional steroids leveled the scars to an inconspicuous appearance. (Courtesy of Dr. C. de Goursac.)

Hives after a Collagen Test Implant

Hives can occur weeks after a test injection in the skin of the forearm. Because this may be an allergic reaction to bovine collagen, a second test on the other arm is recommended.

LATE COMPLICATIONS

Hypertrophic Scarring after Dermal Fillers

Patients who are prone to hypertrophic scarring may react to injected substances in a similar way, but only if it is injected too superficially (i.e., intradermally) (Fig. 12). One patient is known who, after developing hypertrophy of surgical



Fig. 13. Cystic granuloma occurring in both nasolabial folds 3 months after injections of hyaluronic acid. The "sterile abscess" had been drained; the granuloma, however, will remain for 6 to 12 months if untreated.

scars, overreacted to filler implants injected in the correct dermal-subdermal plane.

Granuloma after Injectables

Foreign body granuloma is occasionally seen with all dermal fillers at a rate of 0.01 to 1.0 percent (Table 4). If they occur, they appear after 6 to 24

Table 4. Rates of Foreign Body Granuloma Associated with Various Dermal Fillers

Product	Persistence	Patients	Markets	Granuloma Rates	
				Authors	Manufacturers
Collagen (Zyderm, Zyplast)	6 mo	>5,000,000	U.S. 1982 WW 1983	1:300	1:2500
Hyaluronic acid (Restylane, Hylaform)	6 mo	>2,000,000	Europe 1998 WW 2001 U.S. 2004	1:250	1:2600
PLA microspheres (Sculptra/New-Fill)	>12 mo	>150,000	Europe 1999	1:400 (suspended in 5 ml)	1:500
Ca-HA microspheres (Radiance/Radiesse)	>12 mo	>100,000	U.S. 2004 U.S. 2002		1:50,000
HEMA particles (Dermalive)	>12 mo	>170,000	Europe 2004 Europe 1998	1:80	1:450
PMMA microspheres (Artecoll)	Permanent	>400,000	Canada 2003 Europe 1994	1:800	1:5000
Silicone gel (350 cs)	Permanent	>400,000	WW 1998 U.S. 1953 Banned 1967	1:900	1:1000
Polyacrylamide gel (Aquamid, Bio-Alcamid)	Permanent	>200,000	Russia 1983 China 1998 Europe 2002	1:300	1:5000

PLA, poly-L-lactic acid; HEMA, hydroxyethyl methacrylate; PMMA, polymethylmethacrylate; Ca-HA, calcium hydroxyapatite; cs, centistokes; WW, worldwide.

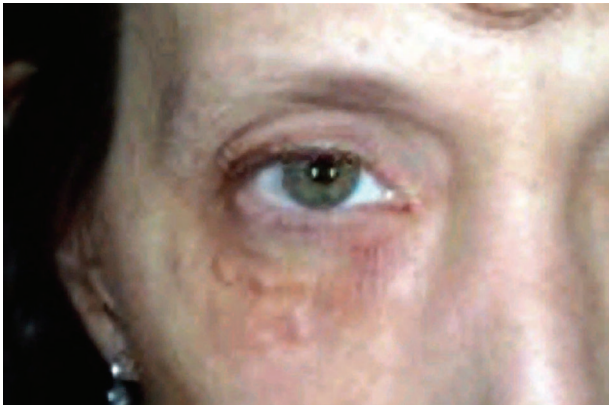


Fig. 14. Typical tiny hard granulomatous papules after Sculptra injection. They did not react to steroids and can be excised through stab incisions.

months at all injected sites at the same time (Fig. 13). The treatment of choice is immediate intralesional steroid injections (Table 5),² not systemic steroid therapy. Surgical excision can be indicated only in small hard Sculptra granulomas (Fig. 14).

Granuloma Resolved and Then Followed by the Same Implant

Foreign body granulomas are not allergic reactions but are caused by a sudden stimulation of the memory of macrophages. We know of two patients who

desired Artecoll after successful treatment of their Artecoll-induced granulomas. Both received second Artecoll injections many years ago, after which neither showed any signs of pathologic reactions.

Late Inflammatory Reactions

Localized redness, swelling, and paresthesia can occur years after injection of any filler, especially in acne scars and vermilion borders. The cause is probably a local irritation, because other injected areas may not be affected. The therapy of choice is intense pulsed light or intralesional triamcinolone.

Lipoatrophy after Injectables

Voy and Mohasseb²⁰ and Andre' et al.²¹ each described five patients who developed a facial atrophy similar to that of human immunodeficiency virus patients under highly active antiretroviral therapy. The condition occurred in both cheeks an average of 9 months after the injection of resorbable fillers (Restylane and New-Fill, and Pro-fill, a polypropylene gel, and later Restylane) into the nasolabial folds. Voy and Mohasseb corrected the depressed deformities surgically through excisions along the nasolabial folds, and Andre' et al. described no treatment.

Ridges in the Dermis

Ridges in the dermis are the result of intradermal injection of a long-lasting filler (Fig. 6). Often in such cases, the filler had been injected correctly (i.e., deep-dermally) but was moved upward by early muscle movement. Keeping the injected site quiet for the first 3 days until encapsulation occurs might prevent early dislocation of implants. This may be achieved by using Botox, a bandage (Fig. 5), or a Velcro band around the forehead or over the lip and around the neck. The best correction is by dermabrasion. A superficial groove should be dug into the implant with the edge of the rotating cylinder, after which the wound will heal nicely without a scar. An alternative is shaving with a scalpel, similar to taking a split skin graft from this ridge.

Steroid Atrophy

This may occur in 5 to 30 percent of patients treated for chronic redness, nodules (Fig. 15), or granuloma, depending on the dose. Some people need 10 times the dose of others to show an effect of steroids. In granuloma, for example, one has to start with a high dose (40 mg of triamcinolone for an entire face) to prevent resistance and recurrences.² The patient has to be aware of this complication, which can be leveled temporarily with collagen or hyaluronic acid until spontaneous recovery occurs. An interesting approach might be repeated intralesional injections of normal saline ranging from 5 to 20 ml per session.²²

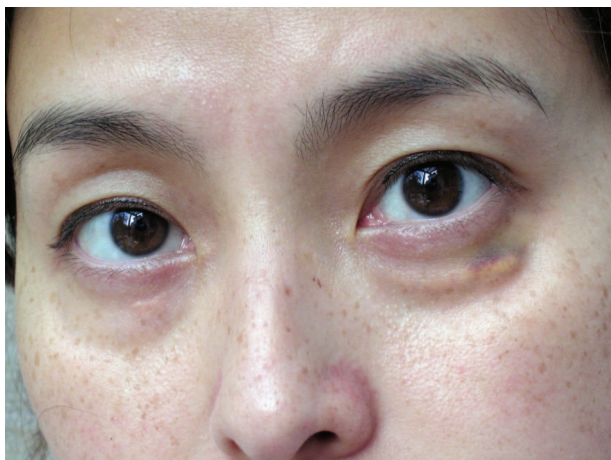


Fig. 15. Steroid atrophy in the left lower eyelid after mistakenly subdermal—instead of epiperiosteal—implantation of Artecoll. This steroid-induced temporary defect could be leveled with a little horseshoe-shaped deposit of collagen.



Fig. 16. (Above) Sclerosing granuloma in both nasolabial folds occurring 8 years after silicone injections. (Below) One intralesional injection of a total of 80 mg prednisolone flattened the granuloma permanently.

Telangiectasia and Granuloma (Fig. 16)

The bluish discoloration of some superficial sclerosing foreign body granulomas can be treated effectively by “flashing” with intense pulsed laser in the same range (e.g., that of the targeting blood vessels). Small noninflammatory granulomas have responded well to long-pulsed 532-nm lasers; larger inflammatory granulomas have shown some favorable responses to 1064-nm long-pulsed lasers. 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.

TREATMENT OF FILLER COMPLICATIONS

Possible early side effects after the injection of a dermal filler, such as swelling, redness, itching, bruising, and bearable pain, have to be discussed with the patients and tolerated by them. The available treatment options have been mentioned above.

Table 5. Proven Treatments for Granulomas

Triamcinolone (Kenalog, Volon-A), 20–40 mg/ml intralesionally
Betamethasone (Diprosone), 5–7 mg intralesionally
Methyl-prednisolone (Depo-Medrol), 20–40 mg undiluted
1/3 Diprosone (1 ml = 3.5 mg) + 1/3 5-fluorouracil (1.6 ml) + 1/3 (1 ml) lidocaine intralesionally
Kenalog (10 mg/ml) + 5-fluorouracil (50 mg/ml) intralesionally

Should cortisone cream be used to treat hardening? All topical creams are absorbed by the first intradermal lymph vessel they reach. Therefore, the effect of this type of treatment on deeper lying implants is very questionable.

Ice Packs

We do not believe that ice packs prevent swelling and bruising. However, they appear to provide a certain comfort to the patient. In a clinical experiment in the early 1970s, 20 patients with blepharoplasties received postoperative warm compresses on their right eye and cold compresses on their left eye, changed continuously over 24 hours. Thirteen patients preferred the cold compresses, whereas seven felt more comfort under warm compresses. Photographs after 4 and 8 days showed no significant difference in swelling and bruising. Unfortunately, no other studies exist on the effect of cold or heat on bruising.

Granuloma

Late granuloma formation (Fig. 15) cannot be predicted. The reason for sudden onset of granuloma may be found in the memory of macrophages, which are suddenly stimulated by a trigger such as a systemic infection.² In a study of an unselected sequential group of nine patients with granuloma, Carruthers and Carruthers²³ found that with conservative management, all granulomas resolved within 2 years. The author found that permanent fillers can cause transient problems but not necessarily permanent problems.

In contrast, a true foreign body granuloma is an overreaction such as hypertrophic scars or keloids and, similar to these conditions, a foreign body granuloma can be treated effectively with intralesional steroid injections. Because of the complexity of granuloma formation and the variety of possible treatment options, we refer the reader to our extensive article in this issue, which describes other possible anecdotal treatment options such as bleomycin, Minocycline, isotreti-

noin, allopurinol, Imuran, Aldara, or tacrolimus cream.²

The basic treatment of chronic inflammation and granuloma are early intralesional steroid injections (Table 5). Despite a 20 to 30 percent skin atrophy rate, the initial dose has to be high (e.g., blanching injections from a 10-mg/ml Kenalog ampule in inflammation, and intralesional injections from a 40-mg/ml Kenalog ampule in granuloma). In both pathologic conditions, as much of the triamcinolone as possible has to be injected. Eventually, the same dose or even a double dose has to be injected again if disappearance of redness or granuloma is not adequate after 3 to 4 weeks.

Starting with low doses of triamcinolone (5 and 10 mg/ml) in granuloma therapy seems to create “resistance” and the risk of resistant recurrence. The combination of triamcinolone, 5-fluorouracil, and lidocaine appears to diminish a risk of skin atrophy, as is probably the case for the combination of prednisolone and betamethasone. All have to be injected in rather high doses,² and the risk of temporary skin atrophy up to 1 year has to be discussed with the patient thoroughly. These depressions, however, can be treated effectively with temporary fillers such as collagen or hyaluronic acids.

CONCLUSIONS

Most adverse events occurring after the injection of dermal fillers can be prevented by proper injection technique. This increases in importance if a long-lasting filler is used, because it will remain beneath the skin. Special attention must be paid to particulate fillers such as Sculptra, Radiesse, silicone, and ArteFill, because they are less forgiving and require knowledge, experience, and a polished technique.

The treatment of complications should be aggressive and initiated as soon as possible after occurrence, either with corticosteroid injections or surgery. It is of the utmost importance to know the clinical and histologic difference between nodules⁸ and granulomas,² because corticosteroids are effective in cellular proliferations but not in nodules of clumped particles or microspheres. Treating complications of dermal fillers effectively, and assuring the patient in the interim before full aesthetic effects are achieved, are the keys to mastering this emerging technology.

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DISCLOSURES

At the time of submission, Gottfried Lemperle, M.D., Ph.D., was a consultant and shareholder of Artes Medical, Inc., San Diego, California, the manufacturer of ArteFill. He currently retains shareholder status only. Peter P. Rullan, M.D., is a clinical investigator of ArteFill and a shareholder of Artes Medical, Inc., San Diego, California. Nelly Gauthier-Hazan, M.D., has no financial interest in any of the mentioned products.

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