Treatment Options for Dermal Filler Complications

The author contends that early adverse reactions to dermal fillers are caused by a superficial injection technique and that late adverse reactions result from unique patient responses. He has found all complications treatable with a correct dose of intralesional steroids or inconspicuous surgical entry. Here he provides guidelines for injection techniques and treatment for complications. (*Aesthetic Surg J* 2006;26:356-364.)

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Excluding the eye, the dermis is the most sensitive organ of the body. Biocompatible filler substances are well tolerated when injected subdermally or epiperiosteally but may cause allergy, chronic inflammation, or even a foreign-body granuloma when injected intradermally. Yet, because wrinkles develop in the dermis, they must be treated in the dermal layer or close to it. Collagen (Zyderm, Inamed, Santa Barbara, CA) and fine dispersed hyaluronic acid gel particles (Restylane Fine Line, Q-Med, Uppsala, Sweden) are exceptions in that they may be injected intradermally without fear of an inflammatory reaction. Permanent and semi-permanent fillers are better injected along the dermal-subdermal junction. Injections into the deeper subcutaneous fat are often lost and ineffective, except for volume restoration (Sculptra, Sanofi-Aventis, Paris, FR).

Rapidly absorbed biological injectables such as collagen or hyaluronic acids are relatively forgiving substances; mistakes made during injection may not be apparent. Longer-lasting substances, such as microspheres from poly-L-lactic acid (Sculptra) or calcium hydroxylapatite (Radiesse, Bioform Medical, San Mateo, CA) or particles from hydroxyethyl methacrylate (HEMA) (Dermalive, Dermatech, Paris, France), must be injected with much more knowledge and caution because possible inflammation, nodules, or granulomas last longer than usual and may be bothersome for years. Permanent fillers such as fluid silicone (Silikon 1000, Alcon Laboratories, Fort Worth, TX); SilSkin (RJ Development, Chester, MO); AdatoSil 5000 (Chiron, Emeryville, CA); polymethylmethacrylate (PMMA) microspheres (ArteFill, Artes Medical, San Diego, CA); or polyacrylamide gels (Aquamid, Ferrosan NS, Copenhagen, Denmark, and Bio-Alcamid Polymekon, Milan, Italy) often require a steep learning curve to treat patients safely and satisfactorily.

Prevention of Complications

Adverse events and complications can be minimized with correct injection technique and selection of injection sites, as well as appropriate patient selection. Contraindications are rare. If a patient has a history of normal wound healing, he or she will well tolerate most injected fillers.

Although clinical and theoretical observations suggest an association between inflammatory processes (such as infections and allergies) with complications following use of permanent fillers,[1] there is no evidence that immune abnormalities are either associated with or triggered by any fillers currently on the market.

Conditions such as multiple allergies, rheumatism, autoimmune diseases, immunodepression or human immunodeficiency virus (HIV) infection, and atrophic or inflammatory skin diseases have still not been proven to be contraindications for treatment with fillers.

It is important to understand the thickness of the facial dermis, which is less than 1 mm in most areas and, surprisingly, increases with age, whereas the thickness of the skin at the extremities decreases.[2] Therefore, the hypothesis that permanent fillers may show through supposedly thin skin in old age is without proof. Permanent implants beneath the nasolabial folds will not become visible even in patients in their 90s. A 26-gauge needle has an outer diameter of 0.5 mm. Therefore, the facial dermis is only twice as thick as the injection needle and has the same diameter as the dermal thickness in a wrinkle. Keeping this in mind, you can find the correct, directly subdermal plane when you see the bulk, but not the gray of the needle.[3] If you can see the "gray" shining through, you are injecting into the dermis.

Table 1. Classification of dermal filler complications

Early side effects	Erythema, redness
	Edema, swelling
	Ecchymosis, bruising
	Acute allergy
	Pain, discoloration
	Under- 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
	Telangectasia
Filler-related complications	Granuloma, "sterile abscess"
	lipoatrophy after injectables

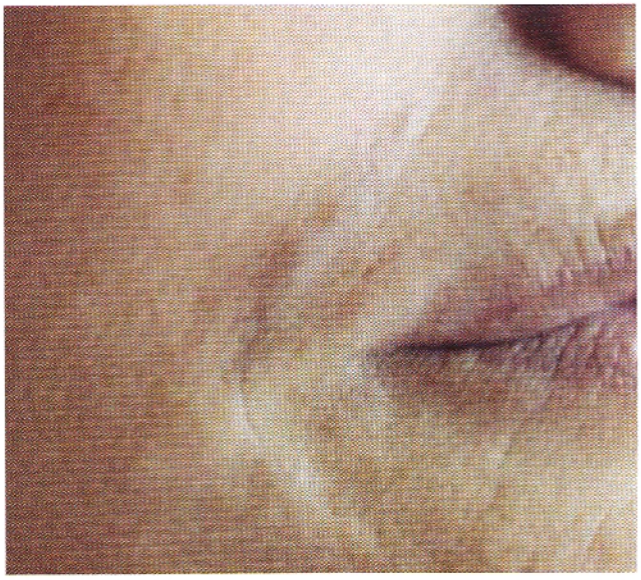

Figure 2. *The ridges in this nasolabial fold appeared shortly after a too-superficial (intradermal) injection of a permanent dermal filler. The ridges can be leveled by dermabrasion or superficial shaving.*

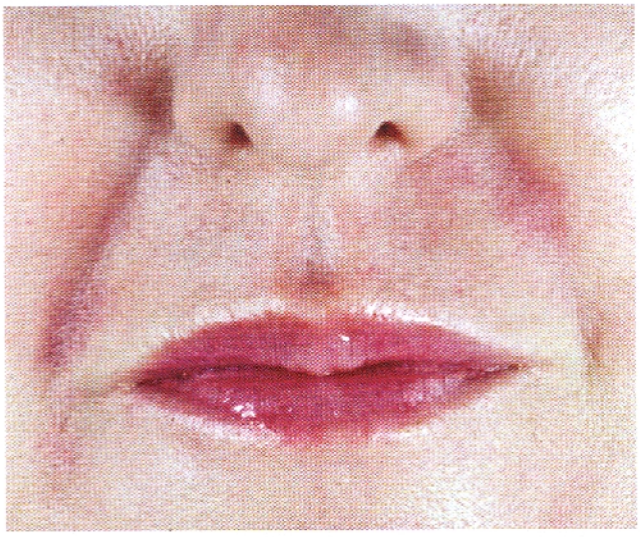

Figure 1. *Redness and nodularity following Zyderm injections disappeared spontaneously several months later.*

Another common mistake is performing intramuscular injection in and around the lips. Constant facial muscle movement, which cannot be prevented during speech and eating, compresses each injected strand to a lump—similar to the muscle of a shell forming a pearl. You cannot know to what location the muscle will dislocate the implant. For example, there is little subcutaneous fat below the corners of the mouth in the marionette line. If the injection is not absolutely subdermal and epimuscular, a lump will be formed by the orbicularis oris muscle. The lump may then appear submucosally inside the mouth. You can get a similar result after filling the subnasal triangle in a plane that is too deep: the superior levator labii muscle will compress the injected material into a "ball" and pull it upwards into the paranasal groove.

All fillers can cause lumps in the lips. Fluid fillers such as collagen, hyaluronic acid, or silicone can be immediately massaged and dispersed into the body of the lip. Particulate fillers such as Radiesse, Sculptra, or ArteFill can be injected as strands into the almost empty space beneath the vermilion border (or "white roll"). However, they should never be injected submucosally as strands or in the body of the lip. Here, the injection of microdroplets, which imitate the size of the mucosal glands, will be a successful technique. A worthwhile addition may be the injection of one IU Botox (Allergan, Inc., Irvine, CA) into each radial lip line 2 weeks before lip augmentation. It will keep the injection site inert for the first 3 days, almost as effectively as a Velcro band (Velcro Industries, Manchester, NH) around the upper lip and neck (Table 1).

Early Complications

Persistent erythema. The side effects common to all dermal injectables include swelling, redness, and bruising, but the most frequent complaint is long-lasting redness (Figure 1). There is no question that the effect of a

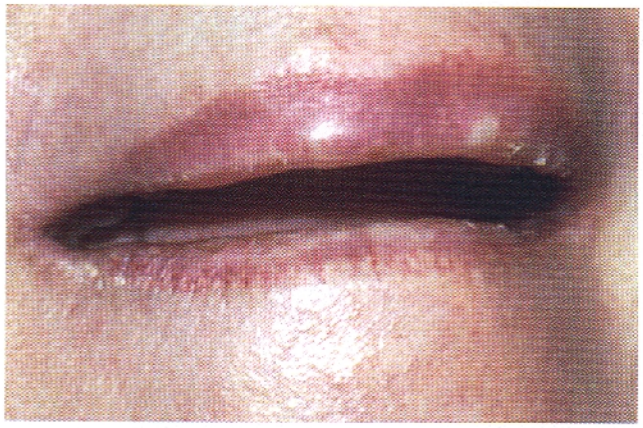

Figure 3. *Typical nodules appear in the lip after injection of longer lasting fillers (silicone in this patient). Nodules can be reduced by intralesional steroid injections or excised individually if disturbing to the patient.*

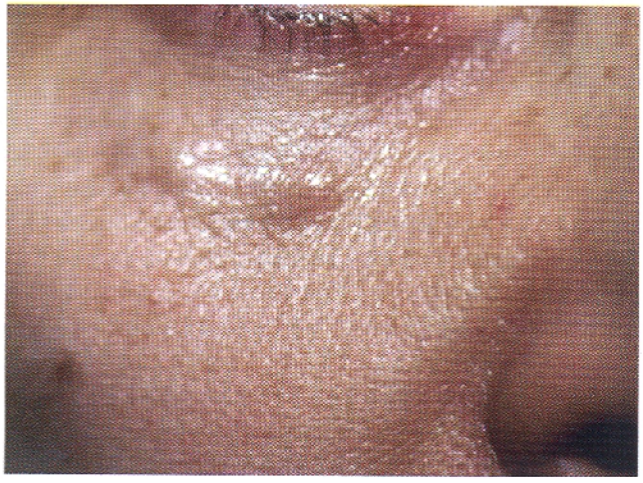

Figure 4. *Nodules appear after implantation of Sculptra in the orbital rim to raise the tear trough. Implantation was accomplished with subdermal injection instead of the correct epiperiosteal injection.*

dermal filler on a wrinkle is optimal when injected as superficially as possible. However, frequently, the reason for posttreatment erythema is the too-superficial (intradermal) injection of the filler. In certain patients who have previously tolerated a filler with no conspicuous adverse events, the dermis may react with inflammation of unknown genesis. The treatment of choice is intense pulsed light (IPL) if the redness is flat. Persistent ridging may require intralesional injections of triamcinolone (Kenalog, Bristol Myers Squibb, N. Billerca, MA), or even better, betamethasone (Diprosone, Schering Plough, Kenilworth, NJ) or methylprednisolone (Depo-Medrol, Pharmacia & Upjohn, Kalamazoo, MI).

Ridge along the injection site. A visible ridge is also caused by an intradermal injection that is too superficial (Figure 2). Ridges do not show up immediately after treatment; if they did, they could be leveled with the injector's fingernail. They form during the first 2 weeks, frequently occurring after treating the nasolabial fold near the ala root with intradermal implants. Constant facial muscle movement appears to separate the intradermal implant (placed into a wrinkle) into 2 strands: one pushed downward into the subdermal fat and one pushed upward into the subepidermal space. Keeping the injected site motionless for the first 3 days until encapsulation occurs may prevent early implant dislocation. Inertia may be achieved with Botox, a transparent tape,[4] or a Velcro band around the forehead, or over the lip and around the neck. To treat this complication, dermabrasion and shave sculpting have been effective. (Shave sculpting is similar to taking a split graft, and the wound will heal nicely without a scar.) Intralesional steroid injections may be effective in "living implants"[3] or implanted "stimulators"[5] such as Sculptra or ArteFill.

Superficial beading. For the same reason that ridges may occur, superficial beading may also occur after intradermal injection. Some beading may be opened early, like a whitehead, and some have to be flattened, using dermabrasion or electrocautery.

Blanching after injection. Blanching is desirable for intradermal fluid injections that dissipate within a few minutes. However, because particulate injectables remain where they are deposited, blanching may not disappear quickly. To avoid a later ridge, it is best to disperse the blanching with the pressure of the thumbnail.

Lumps in the lips. Because of constant lip movement during the first few days following injection (before implant fixation by fibrous encapsulation), lumps in the lips can be formed after administration of all injectables. Early lumps after fluid fillers (or even Radiesse) can be squeezed and massaged into the surrounding tissue. Alternatively, patients can be advised to simply mash the lumps several times a day between two fingers.

Longer-lasting or late-appearing lumps that follow injection of Radiesse,[6] Sculptra, or Dermalive and show little tissue ingrowth are best excised through stab incisions from the inside, since they will persist for years (Figure 3). ArteFill lumps show tissue ingrowth as early as 3 weeks[3]; intralesional Kenalog injections will soften and diminish the nodule by about half of its size.

Distinction between nodule and granuloma. Lumps or nodules (as opposed to granuloma) appear within the first 4 weeks after injection (Figure 4). They are single,

Table 2. Distinction between nodule and granuloma

Characteristic	Granuloma	Nodule
Appearance	Sudden, 6 to 24 months after injection, often inflammatory, telangectasia	One to 2 months after injection, after swelling subsides; noninflammatory[7]
Location	At all injected sites at the same time	Single nodules, close to facial muscles, particularly in the lips
Size	Grow to the size of a bean, accompanied by skin discoloration, edema; rather soft	Remain the same size (similar to a lentil or pea), hard
Borders	Grow fingerlike into surrounding tissue	Well confined by fibrous capsule
Persistence	If untreated, they disappear after 1 to 5 years	Until absorption (or permanent)
Histology	Foreign-body granuloma: droplets, particles, or microspheres are scattered	Foreign-body reaction; particles or microspheres are packed
Treatment	Respond well to intralesional or systemic corticosteroids	Corticosteroids have little effect; must wait for absorption or excision
Cause	Still unknown	Often improper technique or intramuscular injection

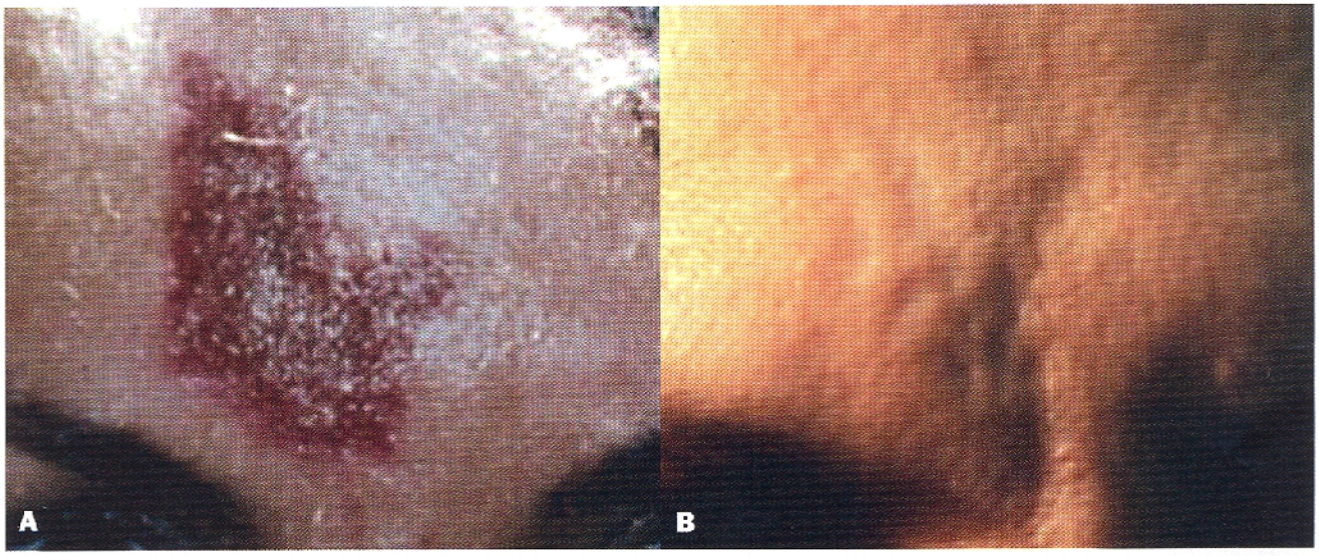

Figure 5. A, *Skin necrosis after injection of Zyplast into glabellar rhytids.* **B,** *Forehead is pictured some months later after slough of the necrotic skin and secondary healing.*

well confined, noninflammatory, do not grow, and are located mostly in and around the lips.[6] True granuloma appear late (most often after 6 to 24 months) at all injected sites at about the same time. They grow rather fast, appear inflammatory, and react well to intralesional steroid injections.[7] The distinction between nodules and granulomas is very important for an immediate and effective treatment regimen (Table 2).[7]

Necrosis as a result of hitting a dermal artery. This serious complication has been observed in glabellar frown lines and oral commissures treated with Zyplast (Inamed, Santa Barbara, CA) (Figure 5). Inamed issued a warning, designating this location a contraindication for Zyplast but not for Zyderm. Necrosis occurs because a superficial branch of the supratrochlear artery, which runs over the corrugator

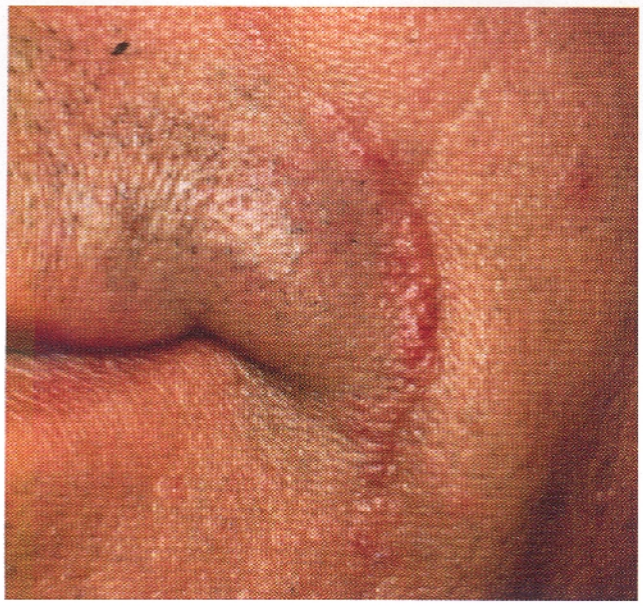

Figure 6. *Hypertrophic scar in one nasolabial fold after a too-superficial (intradermal) injection of Artecoll. The scar became inconspicuous after one intralesional triamcinolone injection.*

and frontalis muscles, can be filled through a resting needle. Reports of skin necrosis after injection of other fillers are rare, since all of these agents are more viscous than Zyplast and can be deposited only in strands (ie, through a constantly moving needle).

Late Complications

Hypertrophic scarring. Patients who are prone to hypertrophic scarring may react to injected substances with scarring, but only if the substance is injected too superficially (intradermally) (Figure 6). However, we do know of one patient with a history of hypertrophic surgical scarring who overreacted to filler implants injected in the correct dermal-subdermal plane.

Late inflammatory reactions. Localized redness, swelling, and paresthesias can occur years after injection of all but temporary fillers, especially in acne scars and vermilion borders (Figure 7). The cause is probably a local irritation, since other injected areas may not be affected. Treatment with IPL or intralesional steroids is frequently effective.[1]

Granuloma after injectables. Foreign-body granuloma may occasionally occur at a rate of 0.01% to 1.0% following injection of all dermal fillers (Table 3). A less realistic number is provided by Saylan,[8] who reported 10 patients injected with Restylane among 500 patients with late developing granulomas (2%), and a 0.4% incidence of early inflammatory reactions. True granulomas can appear simultaneously at all injected sites after 6 to 24 months (Figure 8).[7] The best treatment is immediate intralesional steroid injections as opposed to systemic steroid therapy (Table 4).[7] Late cystic lesions that develop following collagen or hyaluronic acid injections are filled with sterile pus and must be incised and emptied like an abscess. The residual thick capsule is histologically a granuloma,[7] which will respond well to corticosteroid injections. Surgical excision of a granuloma is the last resort and may be indicated in small, hard Sculptra nodules or granulomas if the patient does not want to wait for spontaneous regression (Figure 9).[9]

Steroid atrophy. Depending on steroid dose, this condition may occur in 5% to 30% of patients treated for chronic redness, nodules, or granulomas. Some patients need a steroid dose 10 times stronger than the dose required by others to yield a therapeutic effect. In granulomas, for example, one has to start with a high dose (40 mg of triamcinolone for the entire face) to prevent resistance and recurrences.[7] The patient must be aware of this complication, which can be temporarily leveled with collagen or hyaluronic acid until spontaneous recovery occurs.

Lipoatrophy after injectables. Voy and Mohasseb[10] and André et al[11] reported 5 patients in whom facial atrophy developed in both cheeks (similar to that of HIV patients under therapy). The atrophy occurred about 9 months after the injection of resorbable fillers (Restylane and New-Fill or Profill [OV SA-France], a polypropylene gel) into the nasolabial folds. Voy corrected the depressed deformities surgically through excisions along the nasolabial folds; André did not mention a treatment.

Post-Injection Care

Early side effects after the injection of a dermal filler, such as swelling, redness, itching, bruising, and mild pain, should be discussed with patients. Swelling is a physiological reaction that widens the dermal fibrillar interspaces from a normal maximum of 10 µm to about 20 µm. This facilitates the invasion of histiocytes (which become macrophages) and fibroblasts toward the implant.

Ice bags may feel comfortable to the patient, but their affect on swelling is questionable. In the early 1970s, following blepharoplasty, we tested cold or warm compresses in 20 patients, changing them constantly over 24 hours. The patients received cold wet

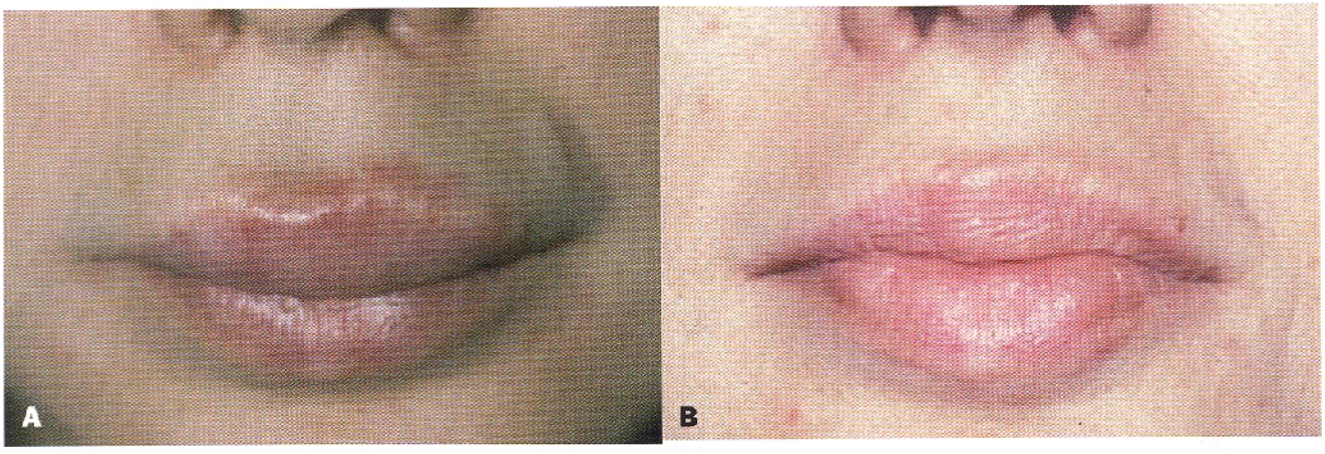

Figure 7. A, *Severe lip edema is associated with a dental infection in a patient who has had silicone augmentation.* **B,** *Spontaneous resolution occurred following removal of the carious teeth.*

Table 3. Granuloma rates associated with different dermal fillers[7]

Product	Persistence	Patients	Markets	Granuloma rates	
				Authors	Manufacturers
Collagen (Zyderm, Zyplast)	6 months	>5,000,000	USA 1982 WW 1983	~1:300	~1:2500
Hyaluronic acid (Restylane)	6 months	>2,000,000	Europe 1998 WW 2001 USA 2004	~1:250	~1:2,600
PLA microspheres (Sculptra/New-Fill)	> 12 months	> 150,000	Europe 1999 USA 2004	~1:400 (in 5 mL)	~1:500
Ca-HA microspheres (Radiance/Radiesse)	> 12 months	> 150,000	USA 2002 Europe 2004		<1:50,000
HEMA particles (Dermalive)	> 12 months	> 170,000	Europe 1998 Canada 2003	~1:80	~1:450
PMMA microspheres (Artecoll)	Permanent	> 400,000	Europe 1994 WW 1998	~1:800	~1:5,000
Silicone fluid (350 cs)	Permanent	>400,000	USA 1953 banned 1967 and 1992	~1:900	>1:1,000
Polyacrylamide gel (Aquamid, Bio-Alcamid)	Permanent	>200,000	Russia 1983 China 1998 Europe 2002	~1:300	~1:5000

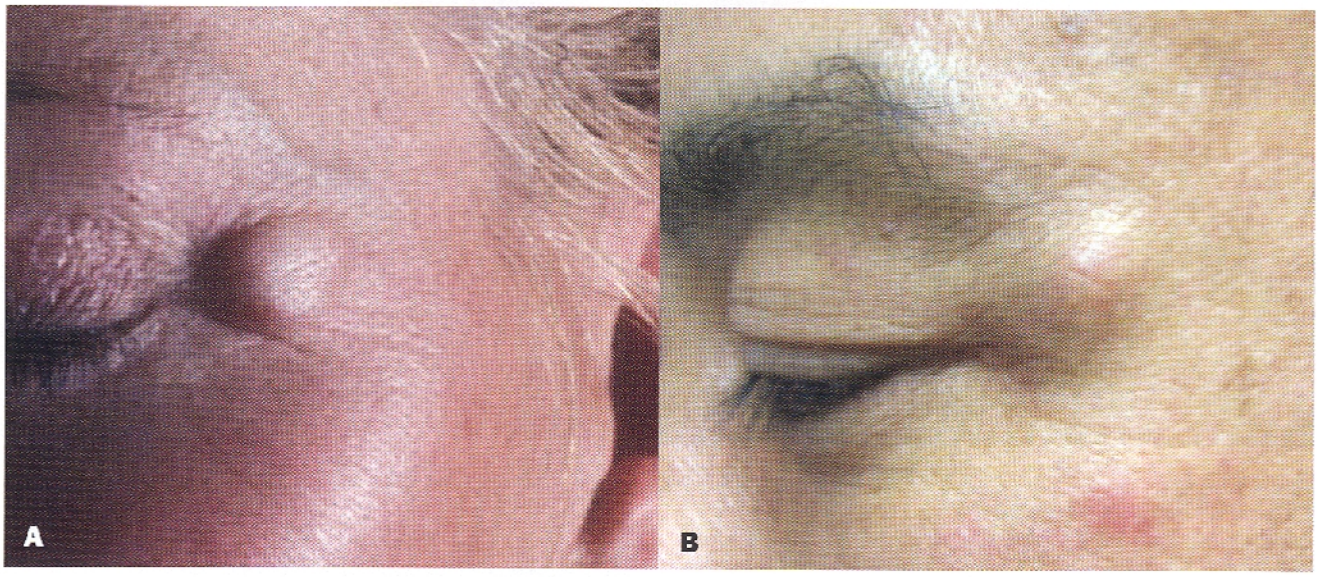

Figure 8. A, *Cystic granuloma in both lid corners is associated with a severe respiratory infection several months after the patient underwent injections of Zyderm I. The patient had a good response to drainage and intralesional corticosteroids.* **B,** *A similar sclerosing granuloma developing in both lid corners in another patient after Artecoll.*

Table 4. Proven treatments for granuloma

Agent	Dose
Triamcinolone (Kenalog; Volon-A, Germany)	20 to 40 mg intralesionally
Betamethasone (Diprosone)	5 to 7 mg intralesionally
Methyl-prednisolone (Depo-Medrol)	20 to 40 mg intralesionally
Diprosone (3, 5 mg) + 5-FU (80 mg) lidocaine	0.5 mL + 1.6 mL + 1 mL intralesionally
Kenalog + 5-FU	(10 mg/mL) + 5-FU (50 mg/mL) intralesionally

compresses on the right eye and warm wet compresses on the left. Thirteen patients preferred the cold compresses, and 7 felt more comfortable with the warm compresses. Photos after 3, 7, and 10 days showed no difference in swelling or bruising using cold or warm compresses.

It is beneficial for patients to maintain a "poker face." Early facial muscle movement during eating, speaking, smiling, and smoking may push the implanted filler strands a tenth of a millimeter deeper into the dermal fat, compromising the wrinkle repair. Patients should limit all facial expressions for about 3 days after injection.

Weather conditions may be significant. Long-lasting swelling of injected lips developed in 2 patients after driving a snowmobile all day in Northern Canada. Therefore, the lower face should be always covered during cold weather sports such as skiing or mountain climbing, and during any other exposure to extreme cold.

Most patients will require 1 to 3 touch-up injections. They should be performed 1 to 3 months after the first implantation if there is no unevenness or asymmetry that may motivate earlier touch-ups. After 3 months, a permanent implant has assumed its final shape, and the wrinkle thickness above it has been restored to the thickness of the surrounding skin.

Treatment of Filler Complications

Late granuloma formation is unpredictable (Figure 8). A sudden onset of granuloma may be attributed to the

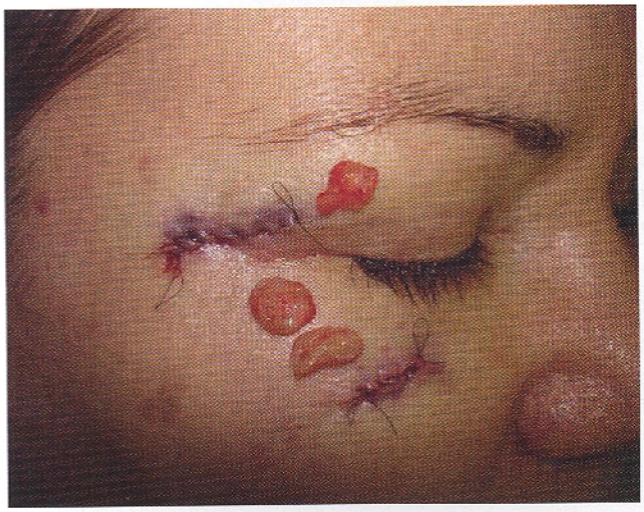

Figure 9. *These excised Dermalive granuloma, close to the orbicularis oculi muscle, show rather well-defined capsules in contrast to other granuloma, which usually show infiltrating borders that are frequently fingerlike.*[6]

memory of macrophages, which are suddenly stimulated by a trigger such as a systemic infection.[1,7] In a study of an unselected sequential group of 9 patients with granuloma, Carruthers[12] found that with conservative management all granuloma resolved within 2 years, indicating that permanent fillers can cause transient, but not necessarily permanent problems. When T-cell function is understood, in both well-integrated implants and those with complications, a rational basis for treatment will be developed.

From another perspective, true foreign-body granuloma may be considered an overreaction, similar to hypertrophic scars or keloids. As such, they may be treated effectively (like hypertrophic scars or keloids) with intralesional steroid injections. For widespread inflammatory granuloma, minocycline is the treatment of choice, along with oral and intralesional corticosteroids. Because freezing seems to soften granuloma, sometimes it may be useful to freeze them before injecting them with Kenalog.

Because of the complexity of granuloma formation and a variety of possible treatment options, we refer the reader to extensive articles on this subject,[1,7] which provide all other possible anecdotal treatment options, such as Bleomycin (Bristol-Myers Squibb, New York, NY); minocycline; Isotretinoin (Barr Pharmaceuticals, Pomona, NY); allopurinol; Imuran (GlaxoWellcome, Auckland, New Zealand); Aldara (3M, St. Paul, MN); or tacrolimus ointment.

The basic treatment for chronic inflammation and granuloma are early intralesional steroid injections (Table 4). Despite a 20% to 30% skin atrophy rate, the initial dose must be high (eg, blanching injections from a 10-mg/mL Kenalog ampule for treating superficial inflammation, and intralesional injections from a 40-mg/mL Kenalog ampule for treating granuloma). For both pathological conditions, inject as many triamcinolone crystals as possible. The same dose, or even a double dose, should be reinjected if disappearance of redness or granuloma is not sufficient after 3 to 4 weeks.

Administering low doses of triamcinolone (5 and 10 mg/mL) in patients with granuloma seems to create resistance and the risk of recurrence. The combination of triamcinolone, 5-fluorouracil, and lidocaine appears to diminish the risk of skin atrophy, as is probably true for the combination of prednisolone and betamethasone. All agents must be injected in rather high doses,[7] and the risk of temporary skin atrophy, up to 1 year, must be thoroughly discussed with the patient. However, temporary skin depressions can be treated effectively with temporary fillers such as collagen or hyaluronic acids.

Summary

All dermal filler substances will cause complications in selected patients. The more superficially the filler is injected, the more pronounced and recognizable the complications. Therefore, most early adverse reactions are caused by an improper injection technique, which may be avoided. In contrast, late adverse events are due to unique patient responses to a filler and/or inherent properties of that filler. Thus, the rate of both inflammatory and noninflammatory foreign-body granuloma differs significantly according to the injectable chosen. Intralesional steroids and, in some patients, oral minocycline can be used to effectively treat most granuloma. There are, however, patients in whom inflammatory granuloma are difficult to treat; most commonly, these are patients who have received high volumes of adulterated silicone or polyacrylamides. All complications are treatable; in most cases it is a matter of finding the right dose of intralesional steroids or an inconspicuous surgical entry.

Injectable fillers are generally safe and well tolerated, but all of them, both temporary and permanent agents, may engender adverse events in some patients. To minimize these, one should be mindful of possible contraindications, discuss outcomes and possible side effects with the patient, practice correct injection tech-

nique, and promptly treat complications if they occur. In most instances complications can be easily and satisfactorily resolved with intralesional corticosteroids or dermabrasion. ■

Disclosure

Dr. Lemperle is a consultant to Artes Medical, Inc., San Diego, CA, the manufacturer of ArteFill, and has stock in this company.

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