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Reversible vs. nonreversible fillers in facial aesthetics: Concerns and considerations

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Abstract

Soft-tissue augmentation of the face is an increasingly popular cosmetic procedure. In recent years, the number of available filling agents has also increased dramatically, improving the range of options available to physicians and patients. Understanding the different characteristics, capabilities, risks, and limitations of the available dermal and subdermal fillers can help physicians improve patient outcomes and reduce the risk of complications. The most popular fillers are those made from cross-linked hyaluronic acid (HA). A major and unique advantage of HA fillers is that they can be quickly and easily reversed by the injection of hyaluronidase into areas in which elimination of the filler is desired, either because there is excess HA in the area or to accelerate the resolution of an adverse reaction to treatment or to the product. In general, a lower incidence of complications (especially late-occurring or long-lasting effects) has been reported with HA fillers compared with the semi-permanent and permanent fillers. The implantation of nonreversible fillers requires more and different expertise on the part of the physician than does injection of HA fillers, and may produce effects and complications that are more difficult or impossible to manage even by the use of corrective surgery. Most practitioners use HA fillers as the foundation of their filler practices because they have found that HA fillers produce excellent aesthetic outcomes with high patient satisfaction, and a low incidence and severity of complications. Only limited subsets of physicians and patients have been able to justify the higher complexity and risks associated with the use of nonreversible fillers.

Perspectives on aesthetic medicine

Aesthetic enhancement has been a human desire throughout recorded history and in all cultures [1]. Treatments to improve facial appearance have ranged from use of cosmetics and topical

agents to surgical intervention, to energy-based therapies (lasers, intense pulsed-light, or radio frequency), and to injectable products – notably botulinum toxin and fillers [2]. These treatments can improve self-perceptions, psychological functioning, and personal and professional interactions with others [3, 4, 5, 6].

Aesthetic procedures to restore, maintain, and enhance one's appearance are almost always voluntary and performed at the request of the patient. Because aesthetic procedures are elective, the ratio of benefits to risks must be very high. Optimal outcomes and patient satisfaction require not only technical skill on the part of the physician, but appropriate patient assessment and education [7]. While patient autonomy in terms of freedom to request a treatment (even if it is not the ideal treatment in the physician's opinion) must be recognized, the physician has a responsibility to refuse requests that have a risk-benefit ratio that is not in the patient's best interest. Physicians also have a responsibility to refer patients elsewhere for consideration of treatments that the physician cannot or prefers not to perform. Patients rely on the physician to act as a "learned intermediary" and to exercise fiduciary responsibility in advising the patient on the best course of action.

In the past, surgical techniques dominated the facial rejuvenation field. Currently, with the availability of nonsurgical procedures that offer cosmetic enhancement and the convenience of minimal downtime, the trend is toward less invasive procedures as well as prophylactic interventions [8, 9]. Restoration of facial volume using fillers can rebalance facial proportions, increase symmetry, and, by reducing wrinkles and volume loss, produce a younger and healthier appearance [8]. Augmentation using soft tissue biodegradable fillers has gained significant market share and continues to increase in popularity, as these products offer more dramatic results than facial creams and chemical peels, yet are safer than non-biodegradable fillers and are less invasive and can be more subtle than facial surgery [10].

The number of filler procedures performed has rapidly increased in the past decade. For example, according to the 2007 Procedure Survey conducted by the American Society for Dermatologic Surgery (ASDS), soft tissue filler injections ranked among the top 5 procedures conducted by ASDS dermasurgeons and soft tissue augmentation procedures showed a 130 percent increase between 2005 and 2007 [11].

Although soft tissue augmentation dates back over a century to when autologous fat was used, injectable fillers entered mainstream cosmetic medicine when bovine collagen injections were developed in the 1980s [12]. Autologous fat, once a staple in the filler arena, has been largely replaced by the new generation of fillers because aesthetic results and duration of benefit after fat injection have a degree of variability that is unacceptable to many physicians and their patients. Reports on the fat-grafting technique are anecdotal and no statistics on the "take" of fat have been published [13].

While physicians had few filling agents (principally fat, collagen, and silicone) a decade ago, they now have a broad range of fillers that vary considerably in physical properties and clinical performance.

Fillers can be classified in a variety of ways ([Table 1](#)). For example, based on source they may be classified as autologous, biological, or synthetic; based on duration of cosmetic benefit they may be short (less than 3 months), medium (3-12 months), long (12-24 months), or very long (more than 24 months). Using reversibility as a criterion, fillers may be classified as very rapidly reversible, slowly biodegradable but not reversible, or nonbiodegradable.

Goals and concerns in aesthetic medicine

Use of dermal and subdermal fillers for facial rejuvenation has become popular because these treatments provide desirable aesthetic outcomes such as a harmonious, attractive appearance without invasive surgical procedures and without the downtime associated with surgery. When performed by a skilled physician and with use of the appropriate filler for the specific application, soft tissue augmentation and dermal filling provide predictable and consistent results.

Cost-benefit optimization from the patient's perspective when both direct and indirect costs are considered is also a factor that has contributed to the popularity of fillers. Risk-benefit considerations of importance to patients include recovery-related downtime; pain and pain-management issues; potential for poor outcomes and their psychosocial and physical impact; and long-term complications and their management.

While no procedure is free from risk or downtime, the appropriate use of fillers is generally associated with lower risk and less downtime compared with surgery or energy-based treatments. It is important to be able to discuss the relative risks and benefits of commonly used fillers and to recognize that some fillers (for example, because of irreversibility or allergenicity) carry an inherently greater risk to the patient.

To reliably obtain successful outcomes, the physician must have a good understanding of facial anatomy, of the material being used, and of the injection technique to be employed. Variables specific to each filler include optimal anesthesia, needle gauge and length, depth of placement, and techniques for management of complications specific to that filler.

Treatment must be individualized, taking into account factors such as the patient's social schedule, budget, aesthetic preferences, expectations and risk tolerance, the patient's skin thickness and texture, facial location to be treated, patient age, and ethnicity. The physician should discuss the relative merits of fillers and other

competing or complementary treatments (for example, botulinum toxin type A [BOTOX®] and surgery), duration of effect, and benefits and risks of each option [7].

The physician must also have the ability to prevent unnecessary discomfort and bruising during treatment, and must be able to recognize and manage complications should they develop during or after treatment. Many leading physicians who administer HA fillers keep hyaluronidase in their offices to correct areas where there is excess HA filler injected by themselves or others, and for use in the very rare instances in which there is a more serious problem, for example, vascular compression or occlusion by an HA filler or an allergic reaction to an HA filler.

Options

Desirable characteristics for dermal filling agents are presented in [Table 2](#) [13, 14, 15]. All commonly used fillers can claim (to varying degrees) to satisfy each of these criteria. In my experience, HA fillers come the closest to truly satisfying all the criteria in this table. Hyaluronic acid fillers have a broader range of facial aesthetic applications and a better risk profile than any one of the nonreversible fillers.

Hyaluronic acid fillers are popular because they offer an excellent balance of efficacy, safety, and duration of cosmetic benefit - and have the unique advantage of reversibility. It is important to keep in mind, however, that there are significant differences among HA fillers. These include feedstock purity, manufacturing processes, HA concentrations, cross-link chemistry, quantity of cross-linkers, and amount of uncross-linked HA-all of which may play an important role in the behavior of these materials during and after injection [16, 17].

Almost all HA fillers on the world market use 1 of 3 basic crosslinking chemistries ([Table 3](#)). Of these 3, butanediol diglycidyl ether (BDDE) has by far the longest track record (about 20 years as of July 2008), and the greatest amount of clinical experience (many millions of patients treated worldwide including North America).

One group of HA fillers that I have found very versatile and reliable over the past several years are the cohesive gel implants. There are several characteristics that distinguish them from the principal alternative, the HA particle slurry fillers. Cohesive gel implants, because of their high viscosity, tend to "stick together" and so remain in the injected area rather than tending to flow into unintended areas as HA particle slurries sometimes do [18]. Because cohesive gel implants are a soft gel rather than a mass of hard particles, they blend into the treated area within a few days, contributing to patient satisfaction, a vital consideration when performing elective aesthetic procedures.

When deciding between competing brands of filler materials,

it is important to consider the critical role played by the manufacturer in both development and marketing of these products, as well as in the continued technical support that helps to maintain and enhance injector knowledge and skill. Successful outcomes depend not just on the relationship between the physician and the patient, but on a relationship that includes the manufacturer of these products. The manufacturer of any medical product must have the resources and integrity to maintain product quality and safety, to properly investigate adverse events, and to market the product and educate physicians and the public about the product in an ethical manner. There are differences in the degree to which various manufacturers of fillers can satisfy these requirements. In some cases, manufacturing and distribution are done by 2 different companies, or even by subcontractors. It is also important to consider how long a product has been on the market worldwide as well as specifically in North America. Because some of the problems with products do not become apparent until after they are marketed, it is often prudent to use products that have been on the market for a number of years and have been used on millions of patients.

After comparing the cohesive HA gel implants available on the Canadian market, I have based my filler practice on a line of BDDE crosslinked HA fillers that are both manufactured and marketed by a company that has a long and excellent business and technical reputation in the aesthetic industry. This gives me high confidence that quality will be maintained and that problems will be quickly detected and effectively dealt with should they arise.

The properties of the various cohesive HA gel implants on the Canadian market are highly variable, and a similar range of such products is likely to appear on the United States market over the next few years. Several years ago, I settled on one family of products that contains a high concentration of crosslinked HA, providing long-lasting, but not permanent, correction, [16] and also contains about 10 percent noncrosslinked HA to optimize flow properties [18]. Because the noncrosslinked HA in this product line is sequestered within the gel mass rather than being free in a vehicle system, there may be fewer adverse experiences, such as nocturnal swelling after injection. The patient's tissues are not exposed to a bolus of free HA as is the case with particle-based HA products [18]. The smooth and cohesive nature of this line of homogenous HA gel fillers encourages gradual and precise filler placement at the appropriate tissue depth.

As with any intervention, soft tissue augmentation with injectable fillers has the potential for a range of complications. Fillers not only differ with respect to chemical composition, dynamics, and interaction with the surrounding host tissue, but also with regard to types and duration of adverse reactions. Adverse effects can be classified as early or delayed and can range from minor complications such as bruising, swelling, tenderness, and skin discoloration, to more serious complications (that can occur with rare but variable frequency in all fillers) such as areas of excess fullness or papules (especially with long-lasting fillers), granulomatous or inflammatory reactions, infection, migration

(especially with some of the permanent implants) [7, 19], and even vascular embolization or compression. Adverse reactions may manifest in the relatively short term (no later than 1 year after injection), the intermediate term (up to 6 years, e.g., after injection of combination gels), and the long term (up to 28 years after injection of silicone gel) [20].

Medium duration and long duration fillers

Because patients and physicians can be misled by the use of terms such as "semi-permanent" and "permanent" fillers, I prefer to use terms that address the issue of greatest interest and concern to patients: duration of cosmetic benefit. Generally, patients care much more about how long they will benefit from treatment than they care about how long traces of the filler material can be found on histologic examination of their skin. To facilitate accurate communication about the expected duration of cosmetic benefit, I describe fillers using the terms "short duration" (less than 3 months, for example bovine collagen implants); "medium duration" (3 to 12 months, for example most HA fillers); "long duration" (12 to 24 months, for example some HA fillers [Juvéderm®] in some circumstances, and, hydroxylapatite [Radiesse®]); and "very long duration" (greater than 24 months of cosmetic benefit, for example silicone, and polymethylmethacrylate microspheres [ArteFill®/ArteSense®]).

To address the need for retreatment and the costs associated with short duration and medium duration fillers, nonreversible and nonbiodegradable long duration and very long duration injectable fillers have been developed for facial augmentation. A number of such products exist: silicone oil (Silikon® 1000), polyacrylamide hydrogel (Bio-Alcamid®); hydroxyethyl methacrylate/ethyl methacrylate fragments in an HA-based vehicle system (DermaLive®/DermaDeep®) or polymethylmethacrylate microspheres suspended in noncrosslinked collagen (ArteFill®/ArteSense®). A suspension of nonreversible but very slowly biodegradable poly-L-lactic acid particles in a solution of mannitol and carbomethoxycellulose (Sculptra®/New-Fill®) [20] is also available.

Although such fillers can provide good outcomes in some circumstances, it is important to recognize that they are less forgiving and less versatile than HA fillers. Complications associated with fillers may require injection of corticosteroids, treatment with systemic corticosteroids, and/or surgical intervention. In some cases (for example, some cases of excessive fullness or inflammatory reactions in the lips secondary to silicone oil, polymethylmethacrylate microspheres, hydroxyethyl methacrylate/ethyl methacrylate, calcium hydroxylapatite, [Radiesse] or porcine collagen gel [Evolence®]) complications cannot be adequately corrected by any intervention. In contrast to these fillers, complications after treatment with HA fillers often will resolve without treatment or resolution can be greatly accelerated

by injection of hyaluronidase [9] and/or by incision of the affected area with a large bore needle and expression of the HA.

Although all cosmetic treatments are technique-dependent, consultation for and implantation of permanent fillers requires different assessment, management, and injection skills than does use of temporary fillers. It can be preferable to use nonpermanent fillers first and then, if the patient wishes, advance to permanent fillers. In addition, as facial contours change naturally with aging, any type of permanent implant that does not naturally change with the rest of the face may become more prominent than desired. A previously satisfactory appearance with a very long-lasting filler can eventually look unnatural [21]. These concerns have been partially addressed with the introduction of very long-lasting fillers such as polymethylmethacrylate microspheres that remodel to some extent as the face ages, thus maintaining a natural look as the years go on (assuming they are initially implanted properly). It is necessary to keep in mind that a patient's dissatisfaction with the aesthetic outcome is apt to be long-lasting, especially if nonreversible, long- or very long-lasting fillers were used as a first treatment approach [21].

None of the nonreversible fillers has the versatility of HA fillers, so users of nonreversible fillers have to keep a broader range of products in inventory. Most practitioners will not perform enough procedures with a permanent filler to maintain the proficiency and expertise necessary to give their patients a high frequency of positive outcomes.

Clinical experience

The following case studies illustrate some of the potential complications associated with the long duration and very long duration (so-called semipermanent and permanent) fillers:

Case study 1

A 47-year-old woman who had nasolabial folds and melomental lines was treated with a total of 0.65 mL of hydroxylapatite (Radiesse®) on each side. She was pleased with the cosmetic result, but 7 months later her dentist noted a flat 1.2 cm white submucosal mass inferior to the right angle of the mouth (Fig. 1). As this was asymptomatic, she was reassured, and it was explained that the mass would probably fade somewhat over the



Figure 1

Figure 1. Submucosal deposit of hydroxylapatite after treatment of nasolabial folds and melomental lines

next year or two. The patient subsequently developed lung cancer, and was unable to return for follow-up.

Case study 2

A 57-year-old woman had nasolabial folds treated with hydroxylapatite 0.65 mL on each side. She was pleased with the cosmetic result, but within a few weeks noted an asymptomatic submucosal 0.8 cm papule deep to the inferior part of the left nasolabial fold. This was photographed 3 months after the treatment (Fig. 2). The papule



Figure 2

Figure 2. Submucosal papule after treatment with hydroxylapatite

persisted and her nasolabial folds were treated again with a total of 1.3 mL of hydroxylapatite 6 months after the initial treatment, because she was pleased with the aesthetic result from the first treatment. The papule was unchanged at follow-up 1 year after the second treatment, after which the patient was lost to follow-up.

Comments. Areas of excess fullness or papules have been reported especially with the long-lasting fillers. In the above-mentioned cases, submucosal deposits of hydroxylapatite resulted in a less than satisfactory outcome for the patients. While the long-lasting dermal fillers provide a longer duration of cosmetic benefit compared with the medium- duration fillers such as the HA fillers, they are less forgiving and complications take considerably longer to resolve. In contrast, with the HA dermal fillers, complications after treatment either resolve without treatment or can be accelerated with hyaluronidase administration.

Case study 3

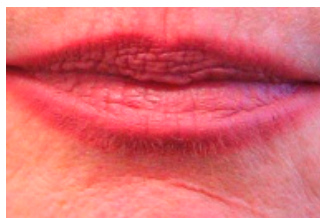


Figure 3a



Figure 3b

Figure 3. Lips pretreatment (a) and 17 days posttreatment (b) with homogeneous polymethylmethacrylate microspheres demonstrating dermal filler movement

The upper lip and lateral lower lips of a 50-year-old woman

were treated with a total of 0.7 mL of homogeneous polymethylmethacrylate microspheres (Artecoll®). Inspection and palpation immediately after treatment were satisfactory, and the patient was pleased. Several hours later, she started to squeeze and reshape the upper lip, apparently moving much of the homogeneous polymethylmethacrylate microspheres into a single mass in the right upper mid lip (Fig. 3b). The mass was injected with 4 0.025 mL doses of triamcinolone acetonide (Kenalog®) 3 mg/mL, and resolved in a satisfactory manner within 2 weeks, with no visible defect and with only a slightly palpable area where the mass had been. One year later, the upper lip was treated successfully with 0.7 mL of homogeneous polymethylmethacrylate microspheres, and the patient (and all subsequent patients) were cautioned against manipulating the lip after treatment with filler substances. Subsequent to this and other adverse events, treatment of the lips with this class of fillers was listed as a contraindication when ArteFill (similar to ArteSense®/Artecoll®) was licensed in the USA.

Comments. Among the variables that influence aesthetic outcomes with fillers, the type of filler and injection site (e.g., lips) are key considerations. Resolution was achieved with this patient using intralesional corticosteroids. This case is a prime example of the need for patient education and counseling prior to dermal filler procedures.

Conclusions

Soft tissue augmentation with fillers is both an art and a science [22]. The extensive array of fillers available requires that physicians develop and maintain a thorough understanding of each product they use with regard to capabilities, limitations, and risk-benefit profile. Appropriate injection technique varies with each filler, and will impact patients' satisfaction and adverse experiences. Physicians who choose to use a variety of filler types will need to spend considerable time developing and maintaining the knowledge and skill necessary to use each product in an optimal manner. As a practical matter in many cases, patients will be better served by optimal treatment with an HA filler than by suboptimal treatment with a nonreversible filler. A physician's skill, combined with appropriate patient assessment and education [7], is the key to successful outcomes.

In aesthetic medicine, patient satisfaction is the principal goal. The number and spectrum of patients seeking minimally invasive facial rejuvenation appears to be expanding. For example, facial aesthetic clinical practices used to treat almost exclusively women, but now an increasing number of men are requesting and undergoing treatment. Recognition of the unique needs of the male aesthetic patient has become important. Occupational and lifestyle considerations, together with differences in skin anatomy, warrant a customized approach; attention to those differences can help physicians create a treatment program that will optimize the

satisfaction of their male patients [23] and maximize positive outcomes.

I strongly encourage practitioners to develop mastery of a range of HA fillers that can provide a broad spectrum of excellent, long-lasting outcomes, have limited complications that are in general readily managed, and consistently produce a high degree of patient satisfaction. The biocompatibility, long-lasting (but not permanent) effects, low incidence of adverse experiences, reversibility, and the versatility offered by the cohesive gel HA fillers make them an excellent and secure foundation for the aesthetic soft tissue-filling practice.

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