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How to Choose Between Options in Soft Tissue Fillers

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Abstract The use of injectable fillers in facial plastic surgery started with injection of collagen and has seen the introduction of numerous fillers over the past few decades. These products are not only used to fill wrinkles, but also for soft tissue augmentation, reconstruction as well as to influence the aging process at a cellular level. It is imperative that the facial plastic and reconstructive surgeon be familiar with the different products available, their recommended uses, and injection techniques. Since these fillers are used predominantly for elective cosmetic procedures, there is an increased burden on the treating provider to ensure patient safety and minimize risk. We provide a review of the different classes of injectables and our recommended treatment algorithms for each.

Keywords Filler · Injectable · Facial rejuvenation · HA · PRP · Filler complications

Introduction

The use of soft tissue fillers and the indications for their use has become a complex topic that we feel privileged to address. The evolution of injectable agents from collagen and fat in the 1980s to the plethora of options in 2014 is astounding in many ways.

Today's agents are not only capable of filling wrinkles, but also may be used for soft tissue augmentation, reconstruction, and cellular modification of the aging process. The aesthetic surgeon needs to target goals for his or her patients' physical improvements based on an understanding of the aging process.

Another important factor to consider is the economic impact of filler injections. For the patient with an unlimited budget and a desire to avoid surgery, multiple different injectables combined with energy devices can produce significant improvement. However, repeating these at regular intervals as the patient progresses through the aging process and/or the fillers reabsorb or dissipate can create a significant ongoing expense.

For the patient with a limited budget, the surgeon needs to target areas that are most bothersome to the patient and work within the realm of economic reality. At some point, surgery that is minimally invasive can become a more viable option.

Another important factor in filler selection is the downtime involved. Clearly some patients are working and trying to improve their professional position or hold on to a job. The need to avoid bruising and limit recovery time can dictate the filler or procedure that a patient undergoes. The flip side of this situation is that more attractive people tend to get hired, and a more attractive appearance can improve a job situation.

Most patients also desire a natural appearance. To overfill a patient and give them an unnatural bloated appearance is undesirable.

While an algorithm for filler injection would be helpful in this day of electronic medical records, an individual aesthetic evaluation of the needs and desires of each patient

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is essential. Nonetheless, certain aesthetic principles can assist the cosmetic surgeon in differentiating between the wide numbers of options.

Is the Primary Problem that Bothers the Patient Volume Loss, Aging of the Skin, or Gravitational Descent?

There is a difference between intrinsic and extrinsic aging that must be taken into consideration. A history of smoking, sun exposure, or stress can indicate that extrinsic aging has produced a countenance that appears older than the stated age. The Glogau classification of photoaging holds for extrinsic aging from other causes as well, and is described in Table 1. The use of appropriate fillers and/or botulinum toxin with or without energy devices, e.g. lasers, may greatly improve advanced photoaging. Bioactive fillers, such as platelet-rich plasma (PRP) applied by injection or microneedling might be of benefit as well [1, 2, 3•].

Differentiating between the loss of volume associated with aging versus gravitational descent is also important. Camouflage of gravitational descent is quite possible with fillers, but when there is severe gravitational descent requiring overfilling, the ultimate effect can produce a bloated and unnatural appearance. A look through the National Enquirer or other "gossip" magazines demonstrates this problem.

Likewise, a significant loss of fat or bony volume requires augmentation to produce a significant improvement in appearance. In this case, correction of gravitational descent without volume augmentation will produce very little improvement.

In the senior author's experience, most patients in their 50s or 60s do not have a great deal of volume loss. Fillers are quite useful to camouflage the soft tissue descent that occurs in these patients. Patients with thin faces or on medications that produce volume loss may be the exception. The distance runner or the HIV facial atrophy patient, for instance, needs consideration for filler correction on a long-term basis.

One way of evaluating volume loss versus gravitational descent in the mid-face is the "*smile test*." When the patient smiles, contraction of the zygomaticus muscle produces a meloplication of the fallen fat pads in the cheek. If the smile produces volume restoration, gravitational descent is assumed. In this case, the concavities and convexities created by the descent should be filled and equalized for camouflage purposes rather than an outright volume augmentation that can produce an unnatural appearance. Over time, many of these patients become interested in surgical intervention after multiple rounds of injections.

To obtain an optimal result, the surgeon needs to look at the face in motion and evaluate each of the patient's anatomic areas. Palpation of the facial structures and a physical examination are essential as described below.

Table 1 Glogau classification of photoaging

Group	Age range	Type	Characteristics
I	20s–30s	Mild	No wrinkles
II	30s–50s	Moderate	Wrinkles in motion
III	50s–60s	Advanced	Wrinkles at rest
IV	60s–70s	Severe	Only wrinkles

The Hylans

Because the hylans (hyaluronic acid or HAs) comprise the majority of the worldwide market for fillers, it is worthwhile to discuss them prior to introducing other fillers. Their ease of use, efficacy, safety profile, and "out of the box" availability have brought them into dominance for most injectable treatment of facial aging. The ability to use hyaluronidase as a reversal agent is another appealing aspect of their use.

Despite their many benefits, they also have side effects and complications that the user needs to be aware of. A filler "crash kit" is critical to have in case of inadvertent inra-arterial injection leading to tissue ischemia (Fig. 1). Side effects of these fillers are primarily seen in the mid-face to upper face. Injections into the nose, mid-face, periocular area, glabella, and temples have produced major complications, such as blindness and ischemic necrosis, when the material enters arteries and occludes them.

Should this occur, copious injections of hyaluronidase into the area or artery involved (including use of ultrasound guidance to assist in intra-arterial placement), oral aspirin, topical nitropaste, and hyperbaric oxygen are indicated. Reports of serious problems are increasing, and units are available at UCLA and other institutions with interventional radiologists and oculoplastic surgeons to assist in treatment. Patients with this type of complication should have treatment rendered as quickly as possible. To minimize these side effects, injections with blunt needles, slow injections with low pressure, and complete avoidance of the glabella are recommended.

Platelet-rich plasma is an alternate injection material for the upper and mid-face that the senior author uses as it is not reported to lead to any complications with inadvertent injection into an artery. Other complications of the HAs include lumps and allergic reactions. The lumps may be injected with hyaluronidase, and bruising may be largely avoided with the use of blunt needles for injection.

Fig. 1 Ischemic tissue of the left upper lip caused by inadvertent injection of HA into an artery of the left upper nasolabial fold

Generally, the HAs last approximately 6 months to a year (as noted in their FDA approval studies in the nasolabial folds), though on occasion 3 year longevity and results approaching permanence can been observed. This is particularly true in areas that do not have a great deal of facial motion, such as the tear trough and eyelid margins.

Often the skin in the perioral area suffers from advanced photoaging, particularly in sun exposed Caucasian females and smokers. This change can be seen quite early in the 30s and 40s. As part of the patient's evaluation, a Glogau classification is helpful. For type II patients (Table 1), filler use is often desired in the nasolabial fold area and for lip augmentation, when early gravitational descent is first noticed. Energy devices [IPL, fractionated CO_2, radiofrequency (RF) microneedles, fractionated RF, etc.] are useful to recondition the skin, along with filler use. Botulinum toxin may also be used in combination with fillers in these areas, specifically in the orbicularis oris and lip depressor muscle areas.

For many patients, HAs are often the treatment of choice. The first HA approved was Hylaform (Inamed, Gauting, Germany and Genzyme, Boston, MA), which was derived from rooster combs. The dominant HAs marketed today are Juvederm (Allergan, Irvine, CA), Restylane (Medicis Aesthetics, Scottsdale, AZ), and Belotero (Merz Aesthetics, San Mateo, CA).

Hyaluronic acid is a complex polysaccharide with cross-linked glucuronic acid and *N*-acytl glucosamine disaccharide units and is uniform from species to species. It is a humectant and attracts water, thus it is present in almost all skin and hair cosmeceuticals. The currently marketed FDA-approved HAs are synthesized by a bacterial fermentation process, and no animal synthesized proteins are available in the US market today.

These products can be differentiated by particle size and their suspension method. Biphasic gels, including Restylane and Perlane (Medicis Aesthetics), are particles of cross-linked HA suspended in liquid. Restylane has a smaller particle size than Perlane, and therefore, more particles per volume (Restylane: 250 μm diameter particle with 100,000 particles/ml, Perlane: 550 μm particles with 8–10,000 particles/ml).

Monophasic gels, including Juvederm Ultra and Juvederm Ultra Plus, are cross-linked in one process (Hylacross), producing a uniform gel without particles. Juvederm Voluma has increased cross-linking and was recently FDA approved for volume replacement of the cheek. Belotero is also a monophasic gel that is produced through polydensified matrix technology yielding increased elastic and viscoelastic properties. These products, while approved for use in the nasolabial folds and lips, are often used off-label throughout the face and neck. The exception is the recent approval of Juvederm Voluma for cheek volumization in the United States.

A rating scale for the severity of the nasolabial folds has been suggested and ranges from 0 to 4, in terms of increasing severity. Types 1–3 are usually improved with filler injection [4]. Type 0 has no need for injection, and Type 4 may require other treatments besides fillers to obtain correction.

Choosing an HA filler for injection may amount to a matter of preference. Juvederm Ultra has a smooth injection feel and passes quite easily through a needle. Injecting physicians performing a large volume of injections may prefer it, as their hands do not get tired from injection pressure. Because it is monophasic and has greater humectant properties, Juvederm can result in volume correction after a few days that is greater than originally anticipated. Juvederm comes in only 0.8 cc syringes, so a disadvantage of this product is that it may require more syringes and more cost to achieve comparable volumization to other products.

Restylane is more of a "what you see is what you get" type of product. It is often more useful in areas that require precise injection, such as around the eye or the tear trough. Some authors feel that it is less smooth, more prone to lumps, and can last longer than Juvederm [5••].

The senior author generally injects Restylane and Juvederm deeply into the superficial subcutaneous tissue and/or lower dermis of the nasolabial fold. This avoids lumpiness and irregularities, and does not seem to influence the product duration of about 6 months to a year. With the HAs, progressive absorption of the product occurs, but the humectant action of the residual HA continues to produce residual fill.

Both Juvederm and Restylane can produce a Tyndall effect causing bluish discoloration when injected into the mid- or superficial dermis. Belotero is considered to have less of this effect due to cross-linking. It can be layered

with other products or upon itself to produce correction of finer wrinkles or wrinkles in finer skin with deep rhytids.

Another tactic used in treating nasolabial folds that are the result of volume loss or gravitational collapse is to first correct the areas of volume loss or gravitational descent in the cheek with a filler. Expansion of the cheek with filler, even in small amounts, may lift the nasolabial folds, so that the folds decrease in depth of sag.

Formerly, collagens were a mainstay of fine perioral wrinkle treatment, and although they are FDA approved, they are no longer available in the United States. Belotero is the current treatment of choice for these rhytids. Off-label, some physicians may dilute Belotero, as much as one to one, to provide a thin solution for fine rhytids. Combination treatments of the upper lip rhytids with energy devices, botulinum toxin, peels, and dermabrasion may be indicated to assist in perioral lip treatments with HAs. When fine rhytids are injected with Belotero, a linear threading technique is commonly used into the upper and mid-dermis.

Perioral rhytids often cause a "lipstick bleed" with the lipstick application migrating into the vertical rhytids surrounding the lips. These rhytids and the lipstick bleeding are frequently improved with injection into the fascial space underlying the white margin of the lip. The filler will migrate up into the rhytids, producing partial fill of the fine vertical lines, as well as lip augmentation.

Belotero, Juvederm, and Restylane are currently approved for use in the nasolabial folds. Restylane is also approved for use in the lips. All other uses of these HAs are off-label, except Juvederm Voluma for cheek augmentation.

The mentolabial folds are an area of concern, particularly as patients progress up the Glogau scale. Gravitational descent and volume loss produce folds in the mentolabial area and a turning down of the corner of the mouth. Injections from lateral to medial in the mentolabial fold area with HAs can turn up the corner of the mouth by extending the injection into the lateral lip. Injections can also be made into the chin line and chin jowl sulcus in a lateral to medial and vertical direction.

Voluma (Allergan) is the newest HA and is a dense version of Juvederm Ultra Plus. It is injected deeply into the cheek area to provide volume. The advantage of this filler is that it is FDA approved for the mid-face, is available off the shelf, and is indicated for the patient with a large budget who wants instant results.

Fillers with Biologic Activity

Sculptra (Valeant Pharmaceuticals, Irvine, CA) is a synthetic polymer originally approved in 2004 for use in HIV patients suffering from lipoatrophy of the face, as well as for aesthetic use in 2009 to correct facial volume loss [6••, 7]. It is characterized as a filler with biologic activity because it causes a local inflammatory response related to hydrolysis of the product along with neocollagenesis and fibrosis in the surrounding tissue.

Another biostimulating filler is Radiesse (Merz), which comprises calcium hydroxyapatite (CaHA) microspheres suspended in an aqueous gel carrier. The carrier eventually dissolves leaving a matrix of CaHA beads that can act as a scaffold for neocollagenesis [6••].

These biostimulatory fillers can be used when contraindications or allergies to other fillers exist, according to patient preference, or when they have been used in the past with success. Radiesse can be injected along the mandible to potentially help form new bone. It can also be used to treat the geniomandibular groove, which may prove to be a more cost-effective approach for patients on a budget since it can result in more long-lasting results.

Despite their numerous advantages, these bioactive fillers can also lead to side effects that can be challenging to manage. Because of their biostimulatory nature, they can cause lumpiness under the skin that is palpable and may be visible and unsightly. Additionally, they can lead to granuloma formation. These issues are compounded by the fact that no agent exists to reverse their effects unlike the HAs.

Permanent Fillers

The only FDA-approved permanent injectable filler is Artefill (Suneva, San Diego, CA), which was approved in 2006. It comprises polymethylmethacrylate (PMMA) suspended in bovine collagen and lidocaine. Unlike previous formulations of PMMA used for years in Europe, which were associated with granulomas, Artefill has a much lower rate of granuloma formation [8]. The permanent fillers are used in the nasolabial folds and should only be used by experienced injectors since there is no reversal agent available, and complications, such as granulomas, are long lasting.

Autologous Fillers

In addition to the synthetic fillers mentioned above, autologous fillers such as fat and platelet-rich plasma are used for correction of volume loss as well. Liporeinjection (autologous fat transfer) seeks to restore lost volume by injecting the patient's fat into areas that have experienced tissue atrophy. Liporeinjection is used for camouflage and volume augmentation both in surgery and independently. However, recently there have been increasing reports of blindness with fat injection into the mid-face, and several centers are investigating this rare complication [9•].

In addition, centrifugation of fat can isolate mesothelial stem cells without treatment with collagenase. Whether there is an advantage to using stem cells with or without other fillers is under active investigation.

Studies have shown that use of PRP can lead to tissue remodeling in photo-aged skin, and clinical trials using activated PRP have shown encouraging and promising results in the rejuvenation of the face and neck [1, 2, 3•]. In the senior author's experience, PRP tends to cause less lumpy filling compared to fat injection and can be used in combination with HAs to form a scaffold to help with wound healing.

Conclusion

Our algorithm for tissue filling is somewhat simple. For the lower face, particularly the nasolabial and mentolabial folds, and the lips, we start by using an HA. For the patient new to fillers, HAs are easy to use and relatively reversible. Tissue necrosis due to intra-arterial injection is rare, but we have a "crash cart" on hand, consisting of hyaluronidase, topical nitrogen paste, oral aspirin, and hyperbaric oxygen availability.

For the patient with prominent mentolabial folds, particularly those with geniomandibular groove deficiency, Radiesse is a consideration. We have not found fat useful in the lower face due to facial movement that can cause irregular reabsorption.

Patients with fine rhytids in the perioral area often benefit from a combination of Belotero and botulinum toxin. Filling the lips with an HA diminishes the lipstick bleed associated with these fine rhytids. We are currently investigating the off-label use of Juvederm Voluma in the lips.

In the mid-face, we discuss options with the patients. For fat and hyaluronic acids, we mention the rare complication of blindness. When informed of this complication, patients often elect not to utilize these fillers. For these patients, we offer PRP, which in our experience provides a uniform fill without lumps due to its diffusion through the tissues with post injection massage.

PRP is our first choice filler for the tear trough and periocular area. We have not observed lumpiness when using PRP, which can be associated with other fillers. PRP can also be used under the eyebrows, particularly at the outer two-thirds to lift the brow. PRP is also helpful to fill in the hollow eye, which can result from over aggressive fat removal during blepharoplasty.

We realize that our algorithms are personal, and certainly, there are other tenable options available. Our approach is to provide the most consistent and natural results in the safest way possible. Because these are elective cosmetic procedures that most patients regard as a minor treatment, there is an increased burden on the medical professional to minimize risk and keep patient safety at the forefront.

Compliance with Ethics Guidelines

Conflict of Interest Andrew D. Beckler and Gregory S. Keller declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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