Journal of Plastic, Reconstructive & Aesthetic Surgery (2009) 62, 11–18

JPRAS
An International Journal of Surgical Reconstruction
www.JPRASurg.com

REVIEW

Injectable fillers for facial rejuvenation: a review

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Received 17 August 2007; accepted 9 June 2008

KEYWORDS
Facial fillers;
Dermal fillers;
Injectable facial fillers;
Dermal implants;
Soft-tissue augmentation;
Facial rejuvenation

Summary Health care practices are moving toward a more preventative focus. In addition to leading healthier lives and seeking help to eradicate disease, patients are enlisting the help of plastic surgeons to reduce the visible signs of aging. Traditionally, facial rejuvenation focused on skin tightening through resection and resurfacing. In recent years, increasing emphasis has been placed on minimally invasive cosmetic improvement. Today, plastic surgeons combat the effects of aging with a variety of non-incisional methods such as soft-tissue augmentation with facial fillers. A multitude of soft-tissue fillers exist, each with their own chemical constituents, indications, and effectiveness. It is imperative that plastic surgeons understand these agents when treating patients with cosmetic complaints.

Health-care practices are moving towards a more preventative focus. In addition to leading healthier lives and seeking help to eradicate disease, patients are enlisting the help of plastic surgeons to reduce the visible signs of aging or being unwell. According to the American Society of Plastic Surgeons (ASPS), from 1992 to 2002, the number of cosmetic procedures performed in the United States has increased by 393%.[1,2] This increase includes both surgical and non-surgical procedures and reflects worldwide trends.

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The process of aging is complex, involving three important factors: global facial volume loss, dynamic and static wrinkles and folds caused by the repetitive movement of facial muscles and laxity induced by the force of gravity.[3,4,5] Generally, the process becomes apparent in the mid- to late thirties when the eyelids droop, and wrinkles and fine lines appear around the eyes and mouth. As one enters the fifties and sixties, the wrinkling continues, the jaw line begins to sag and the neck and nasal tips droop.

Traditionally, facial rejuvenation has focussed on skin tightening through surgical resection and superficial skin resurfacing. In recent years, a major shift in facial rejuvenation has occurred, with increasing emphasis on minimally invasive cosmetic improvement.[2] Currently, plastic surgeons combat the effects of aging with a variety

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doi:10.1016/j.bjps.2008.06.036

of non-incisional methods, such as soft-tissue augmentation with facial fillers. A multitude of soft-tissue fillers exist, each with their own chemical constituents, indications and effectiveness. A thorough knowledge of the properties of facial fillers is imperative for plastic surgeons treating patients with cosmetic complaints.

This article is an overview of the most common facial fillers used for facial rejuvenation, including their descriptions, recommended indications, advantages and disadvantages.

Background

The search for the ideal facial filler began more than a century ago. Soft-tissue augmentation dates back to 1893, when Neuber first described autologous fat transfer for facial defects.[6] Just a few years later, paraffin was injected for cosmetic enhancement. This technique enjoyed considerable popularity, until patients began to develop severe foreign-body and granulomatous reactions.[7] The use of liquid silicone for cosmetic purposes began in Germany, Switzerland and Japan in the 1940s. Beginning in the 1960s, it was also being used successfully in the United States. Despite its success as a soft-tissue filler, reports of significant complications and adverse events have precluded its approval for cosmetic purposes by the United States Food and Drug Administration (FDA) as well as by countries within the European Economic Area (EEA).[8,9]

In the 1980s, the use of bovine collagen for cosmetic purposes started a new era of soft-tissue augmentation. Over the past 5 years alone, the number of approved facial fillers in the US and abroad has grown rapidly. To date, the most widely used products fall into four major categories: autologous fat, collagens, hyaluronic acid (HA) and biosynthetic polymers. These injectable facial fillers are created either in the laboratory or are harvested from the patients themselves (autologous implants), another human (allogenic implants) or an animal or bacterium (xenogenic implants).

In addition to the categorical differences described above, facial fillers can be grouped according to their degree of permanence after injection. Non-permanent fillers produce short-lived results and eventually undergo resorption. Fillers of this type will require repeated injections for long-term results. Semi-permanent fillers typically last longer than most non-permanent fillers, but can be expected to experience some resorption as well. Only permanent fillers can be expected to produce long-term results with a single injection. As the name implies, these products will persist within the tissue indefinitely — a characteristic that might raise concerns regarding safety and the potential for long-term side effects.

A common misnomer with respect to injectables is one that labels all fillers as 'dermal' fillers. Although many of the products for use on superficial defects are injected directly into the dermis, some fillers, namely, the biosynthetic polymers and products more appropriate for deeper defects, are more accurately termed subcutaneous soft-tissue materials. This distinction is important given that products which are preferentially used for deeper defects should not be injected within the dermis in order to avoid palpability and the risk of permanent nodularity and/or contour abnormalities.

Although injectable facial fillers can offer an efficacious alternative to surgery for the aging face, they also have their limitations.[2,3,10–12] It is important for the plastic surgeon to recognise specific circumstances which may be best managed with an alternative to fillers, including superficial contour defects too shallow for fillers, areas with significant skin laxity in which filler injection may result in lumpiness and deep defects or folds in areas of dynamic movement which may result in filler dislodgement or visible filler implants.

When using injectable facial fillers, it is important to remember the exhortation to 'avoid doing harm'. The ideal filler should thus satisfy the following three conditions:

I Safety: It should be non-immunogenic, non-carcinogenic, non-teratogenic, non-infectious and have low abuse potential.
II Efficacy: It should look and feel natural and show reproducible long-term benefit.
III Practicality: It should be cost-effective, easy to use, and removable (or self-remitting) if required or desired.[10,13]

Technique and post-procedural considerations

Most injectable fillers are supplied with a syringe and needle. The needle size, which is generally determined by filler viscosity, can be exchanged with an alternate choice based on the surgeon's experience. Generally, the smallest needle that can deliver the filler appropriately is the ideal choice to limit pain upon injection.[10]

For injection, the needle depth is dependent on the defect or wrinkle depth. Superficial defects require shallow injection, with the needle tip barely entering the skin, whereas moderate and deeper defects require injections at the level of the mid- or deep dermis or at the dermal–subcutaneous junctions, respectively. Blanching typically occurs with superficial and sometimes, moderate-depth augmentation. Gentle massage of the product after insertion can ensure an even correction; however, it is important to avoid aggressive or prolonged massage, which can lead to product displacement.[10] As a general rule, the greater the depth of the defect, the higher should be the viscosity of the products used; less viscous materials are more appropriate for shallower defects.

There are four commonly reported techniques for filler injection: serial puncture, threading, fanning and cross-hatching (Figure 1). There is currently no algorithm for choosing an injection technique. While certain situations may lend themselves to a particular technique, this decision is typically surgeon dependent and related to experience, defect size and location, as well as the particular filler being used. In the serial puncture technique, the skin is held taut and the needle is inserted up to the appropriate depth. The product is then delivered in a small bolus to fill the defect, following which the needle is removed. The needle can then be reinserted along a particular defect and a new bolus injected. This technique is often used for lip augmentation or superficial placement of fillers along a particular wrinkle. In

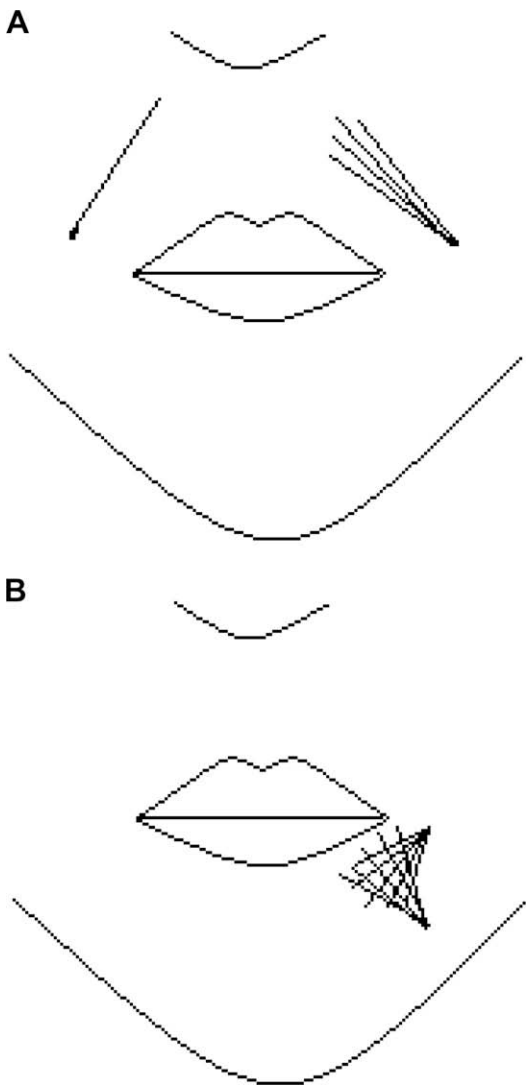

Figure 1 Diagram of common filler injection techniques. A. Threading and Fanning — In the threading technique, the needle is tunnelled through a defect at the appropriate depth, and the filler is injected as the needle is withdrawn. In the fanning technique, multiple threads are injected using a single insertion point without removing the needle from the skin. B. Cross-hatching — The fanning technique is used with a secondary injection point occurring perpendicular to the primary injection threads. This technique is useful for injection of larger defect areas.

the threading technique, the needle is inserted into the defect and tunnelled through at the appropriate depth. As the needle is being withdrawn, the product is delivered in a slow, continuous stream.[10] This technique is commonly used for lip augmentation as well as nasolabial fold injection. The fanning technique is similar to the threading technique, but the direction of the needle is continually changed in a radial fashion, and new lines are injected without withdrawing the needle tip. Cross-hatching involves a series of threads injected in a perpendicular fashion to each other. The fanning and cross-hatching techniques are generally used to fill larger defect areas.[5]

Following injection, several post-treatment guidelines are recommended. [5,10] Cold compresses can be applied, and if desired re-applied, for 24—48 h to reduce swelling. Strenuous physical activity should be avoided immediately after injection. Patients should also be told to minimise aggressive facial movement or massaging/manipulation for several hours after implant placement. They should avoid excessive sun exposure until superficial erythema and swelling disappears. If prudent, for instance, in patients with a history of cold sores or susceptibility to infection, antibiotic or antiviral courses should be considered. Aspirin, non-steroidal, anti-inflammatory drugs (NSAIDs) and/or other blood-thinning medications, including herbal medications, should be avoided for 24—48 h before and after injection, unless they are necessary for patient well-being.

Facial fillers

There are currently many soft-tissue fillers are marketed (Table 1). In general, these fillers fall within one of the four major categories: autologous implants, collagens, HAs and biosynthetic polymers.

Autologous fat

After Neuber's initial use of autologous fat for soft-tissue augmentation in 1893, the use of fat for cosmetic purposes declined until the late 1970s. This initial decline was most likely due to the limited reproducibility of results; however, with the advent of suction lipectomy and improved harvesting techniques, autologous fat grafts have regained popularity.[10,14] Overall correction and duration are similar to that of bovine collagen, although a high rate of resorption can occur.[14,15]

Collagens

Collagen is a major component of human connective tissues, such as bone, cartilage, skin and vasculature. The injectable forms consist of varying concentrations of purified bovine or human collagen. Bovine collagen is harvested from cattle skin. It was the first FDA-approved product for soft-tissue augmentation in the United States. Prior to the advent of HA fillers, collagen was the 'gold standard' injectable filler.[10] Human collagens are derived from cadavers or laboratory cultures of human fibroblast cells. These collagens have gained popularity due to the reduced risk of hypersensitivity and immunological reactions as compared to their bovine counterparts (Table 1).[10,11,16]

Hyaluronic acids

HA is a major component of connective tissues, especially the human dermis. It is a naturally occurring compound that provides a scaffold for collagen development. The main functions of HA include hydration, lubrication and stabilisation of connective tissues. As the skin ages, the amount of HA within the connective tissues decreases — leading to reduced cell hydration, elasticity and movement. In the natural form, injectable HA lasts only 1—2 days secondary

Table 1 Common facial fillers currently available for use in soft-tissue augmentation

Filler Type	Name *(Manufacturer)*	Indication	Durability	Advantages	Disadvantages	Market Status
Autologous Products	Viable Fat	Deep defects	Variable — months to years	Abundant supply, safe, inexpensive	Donor-site morbidity, variable reproducibility, requires processing	No FDA/EEA approval required
	Autologous Collagen/ Autolagen *(Collagenesis, Beverly, MA; Isolagen, Exton, PA)*	Moderate to deep defects	Months to years	Processed from excised skin, can be stored up to 6 months, safe	Donor morbidity, painful, costly	FDA approved / CE mark
Bovine Collagens	Zyderm 1 (3.5% dermal collagen) *(INAMED, Santa Barbara, CA)*	Superficial defects, fine lines, acne scars	2—4 months	Safe, reliable, contains lidocaine, ease of administration	Allergic reaction in 1—3%, short-term results, requires skin testing prior to use, reactivation of herpes is possible with lip injections	FDA approved/CE mark
	Zyderm 2 (6.5% collagen) *(INAMED, Santa Barbara, CA)*	Moderate defects, deeper acne scars, lip augmentation	2—6 months	Same as Zyderm 1	Same as Zyderm 1	FDA approved/CE mark
	Zyplast (3.5% cross-linked collagen) *(INAMED, Santa Barbara, CA)*	Deep defects, lip augmentation	2—6 months	Same as Zyderm 1, more viscous and resistant to degradation	Can cause skin necrosis if used in glabella, allergies in 3%, requires skin testing	FDA approved/CE mark
Cadaveric Collagens	AlloDerm (acellular human dermis, comes in sheets of varying sizes) *(LifeCell, Branchburg, NJ)*	Deep wrinkles or scars, lip augmentation	6—12 months	Safe, No allergy testing required	Expensive, surgically implanted, often causes temporary swelling, occasionally palpable, shrinkage with time	FDA approved/CE mark
	Cymetra (micronized, injectable form of AlloDerm) *(LifeCell, Branchburg, NJ)*	Deep wrinkles or scars, lip augmentation	3—6 months	Safe, No allergy testing required, contains lidocaine	Can cause skin necrosis if used in glabella, costly, often clumps within needle	FDA approved/CE mark
Cell-cultured collagen	Cosmoderm (35 mg/mL collagen) *(INAMED, Santa Barbara, CA)*	Superficial defects, shallow wrinkles and acne scars	3—4 months	Safe, No allergy testing required, contains lidocaine	Short-term results, the more common side effects include cold symptoms (4%), flu symptoms (2%)	FDA approved/CE mark
	Cosmoplast (35 mg/mL cross-linked collagen) *(INAMED, Santa Barbara, CA)*	Deeper defects and wrinkles, lip augmentation	3—4 months	Same as Cosmoderm	Same as Cosmoderm	FDA approved/CE mark

Avian-derived Hyaluronic Acids	Hylaform gel *(INAMED, Santa Barbara, CA)*	Moderate defects, lip augmentation	3—4 months	Safe, reliable, no allergy testing is required	Short-term results, immunologic reactions in patient allergic to avian products (eggs)	FDA approved/CE mark
	Hylaform Plus *(INAMED, Santa Barbara, CA)*	Moderate to deeper defects, facial wrinkles, and folds.	3—4 months	Same as hylaform gel	Same as hylaform gel, superficial injection may lead to skin discolouration	FDA approved/CE mark
Bacterial-cultured Hyaluronic Acids	Restylane/ Restylane Fine *(Medicis, Scottsdale, AZ)*	Superficial (Restylane Fine) to moderate defects, deeper wrinkle reduction, nasolabial folds, glabellar creases, lip augmentation	6—12 months	Safe, reliable, predictable results, no allergy testing required, longer lasting than bovine collagens	Rare immunologic reactions, higher incidence of bruising, pain, and post-procedure swelling vs. bovine collagens, higher cost	FDA approved/CE mark
	Perlane *(Medicis, Montreal, Canada)*	Deeper defects, shaping facial contours, lip augmentation	6—12 months	Same as Restylane	Same as Restylane	FDA approved/CE mark
	Captique *(INAMED, Santa Barbara, CA)*	Superficial defects, fine lines and wrinkles	3—6 months	Safe, no allergy testing required, similar to Restylane	Relatively new product, short term results	FDA approved/CE mark
	Juvederm 18, 24, 30 *(L.E.A. Derm, Paris, France)*	Superficial (18), moderate (24), and deep (30) defects	3—6 months	Safe, predictable results, no allergy testing needed	Short term results, rare immunologic reactions, relatively new product	FDA approved
Synthetics	Sculptra (poly-L-lactic acid microparticles) *(Dermik Laboratories, Berwyn, PA)*	Deep defects	1—2 years	Long term results, safe	Rare foreign body reaction, limited US results studies	Approved for lipoatrophy; off label for cosmetic purposes/CE mark
	Radiesse (Calcium hydroxyapatite microspheres) *(Bioform Medical, Franksville, WI)*	Deep defects, nasolabial folds, vertical lip lines, acne scars, marionette lines, volume restoration around cheeks	1—2 years	Long-term results, no allergy testing required, no concern for antigenic or inflammatory reactions	Can rarely develop nodules if injected superficially	FDA approved/CE mark

(*continued on next page*)

Table 1 (*continued*)

Filler Type	Name *(Manufacturer)*	Indication	Durability	Advantages	Disadvantages	Market Status
	Artecoll/ArteFill (polymethylmethacralate microspheres in 3.5% bovine collagen and 0.3% lidocaine) *(Artes Medical, San Diego, CA)*	Deep defects, glabella, nasolabial folds	Permanent after nearly 50% resorption	Unrivaled longevity, probably safe, but reports of persistent erythema at injection site	Palpable if placed superficially or excessively — thus avoid injecting into the lips and areas with thin overlying skin, requires allergy testing	Preliminary FDA approval for cosmetic purposes/CE mark
	Reviderm Intra (Dextran beads in a hylan gel) *(Rofil Medical International, Breda, The Netherlands)*	Deep defects, lip augmentation	Months to years	Long-term results, safe	Post-procedural swelling, relatively new product to USA	Not FDA approved/CE mark
	Silicone/Silikon-1000 (liquid silicone) *(Alcon Laboratories, Fort Worth, TX)*	Deep defects, lip augmentation	Permanent	Permanent, safe, long clinical experience	Migration, foreign body reactions, poor reputation	Off label for cosmetic purposes
	Endoplast 50 (Elastin and Collagen) *(Laboratories Filorgra, Paris, France)*	Deep defects, lip augmentation	12 months	Long-term results	Allergy tests required, limited experience	Not FDA approved/CE mark
	Bio-Alcamid (96% water, 4% poly-alkyl imide) (*Pur Medical Corp, Toronto, Canada)*	Deep defects	Permanent	Long-term results, removable, no allergy testing required, bio-compatible	Limited experience, inflammatory reactions, infectious complications, migration	FDA approved/CE mark for HIV lipoatrophy
	Aquamid (polyacrylamide hydrogel) *(Contura International)*	Deep defects, lip augmentation	Permanent	Long-term results, compound plasticity	High rate of granuloma formation, infectious complications	Not FDA approved/CE mark

Adapted from Johl,[3] Murray,[10] Broder,[13] Eppley,[11] Sengelmann.[19]

to local degradation. Biotechnical companies have been successful in creating stabile HA molecules with longer-lasting effects.[5,10,17] Most plastic surgeons would agree that the HA filler, Restylane, is currently the most commonly used facial filler worldwide (Table 1).

Synthetic polymers

Synthetic compounds have gained favour as soft-tissue augmentation agents for several reasons: cost-effectiveness, consistent formulation with the possibility for mass production, limited immunogenicity and the potential for permanent and/or long-term effects. One of the first synthetics on the market was silicone. Despite excellent cosmetic results, problems with migration and foreign-body reactions have precluded FDA and Conformité Européene (CE)-mark approval for cosmetic purposes.[8,9] In general, synthetic facial fillers are composed of a biosynthetic polymer (e.g., poly-L-lactic acid, calcium hydroxyapatite and polymethylmethacralate) combined with differing injectable carriers, including hydrogels, beads and liquids.[4,10,11]

Although synthetic polymers may lead to more permanent results, they may also raise concerns over long-term side effects or adverse events. One such product gaining wide popularity among plastic surgeons in the Far East is Aquamid, a polyacrylamide hydrogel. Several large case series in the literature have reported a high rate of adverse events with its use, primarily granuloma formation and subclinical infections, raising concerns over long-term safety (Table 1).

Facial filler complications

As with any procedure, surgical or non-surgical, soft-tissue augmentation is not without risks. Many complications have been reported with facial filler use.[12,18] In fact, interpreting the literature for a particular filler can be frustrating, as it is common to find multiple case series with contradictory efficacy and side effect profiles. It is unclear as to the exact aetiology of these contradictions; however, surgeon inexperience with filler injection, improper patient selection, and defect/filler mismatch likely play an integral role. Although most side effects to facial fillers are transient and minor in nature, it is important to discuss these complications with patients prior to injection.

Bleeding is commonly associated with patient anticoagulation due to concurrent and/or recent use of aspirin, NSAIDs or blood-thinning medications. In addition, the use of large-bore needles and injection into highly vascular areas, such as the lip, can also increase the risk of bleeding.[10,19]

Infectious complications are rare; however, patients with susceptibility to infection or a history of herpes simplex infections may be candidates for prophylactic antiviral and/or antibacterial therapy.[10]

Acute allergic reactions are a serious concern for fillers containing bovine and other xenogenic components.[3] To minimise this risk, product recommendations for allergies and allergy testing should be followed. Patients who have had a prior hypersensitivity reaction to a specific filler should not, again, be treated with that filler. Given the availability of injectable human collagen, allergy testing prior to bovine collagen injection is now mostly of historical interest.[10]

Post-injection pain is common and can be reduced using the smallest needle possible for injection. For less viscous fillers, this may be a 30-guage or 32-guage needle; more viscous fillers may require a 27-guage needle (e.g., calcium hydroxylapatite), or even a 25-guage needle (poly-L-lactate) to avoid clumping or clogging.[4,20] Topical or regional anaesthesia, including nerve blocks, can be used when required. Some injectables may contain small amounts of lidocaine as part of their injection carrier. Caution should be employed when using local injectable anaesthesia as this may alter and obscure the contour defects.[10]

In general, all fillers create some form of histological reaction that generally evolves over time.[21] This inflammatory reaction is of particular concern for the semi-permanent and permanent fillers as its persistence may lead to a more chronic inflammatory process. More severe granulomatous reactions can also occur and have been reported even with more biologic products, such as the HAs.[3] Granulomas can often be treated with simple excision.[22]

Improper injection technique can also lead to complications. If filler is inappropriately injected at the incorrect skin depth, location or volume, a myriad of unwanted skin changes can occur, including palpable bumps, contour deformities and superficial beading.[10] These unwanted changes may resolve slowly.

Of the common injectable fillers, only Cosmoderm or Zyderm is appropriate for superficial injections so as to cause a florid white blanch. Significantly, initial reports have shown that laser or energy-device treatment over soft-tissue augmentation materials appears not to damage, deform or destroy the implants or cause adverse tissue reactions.[23]

Serious complications are rare, but can include anaphylactic reactions, skin necrosis, blindness and death.[10–12,18,19]

Injectable facial fillers offer an excellent option in the treatment of facial aging, wrinkling and contour defects. They are a viable alternative to surgery for patients seeking a safe, minimally invasive and affordable means of maintaining a youthful appearance. It is imperative for the plastic surgeon to have a thorough knowledge of all the available products and their properties. This knowledge will enable optimal pairing of facial filler with specific defects and consequent maximal efficacy and patient satisfaction.

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The Editor would like to thank the following people who acted as peer-reviewers in 2008.

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