An Overview of Injectable Fillers With Special Consideration to the Periorbital Area

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The use of temporary fillers continues to grow as the understanding of restoring a youthful appearance expands. Improving the signs of aging using only surgical techniques has transitioned to treatment of soft tissue atrophy with volume replacement. Temporary fillers have given many patients a lower cost, less permanent introduction into optimizing their appearance at any age. In this article, we explore the history of temporary fillers and the current types that are available. We also highlight the expanding use of injectable fillers in the upper face and periorbital area.

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HISTORICAL OVERVIEW

Over the last few decades, soft tissue augmentation with temporary fillers has become increasingly popular, safe, and effective in providing a more youthful appearance. Several injectable fillers are available, including hyaluronic acid (HA), calcium hydroxylapatite (CaHA), and poly-L-lactic acid (PLLA). The ideal characteristics of a filler include biocompatibility with a low incidence of adverse events (AEs); simplicity of preparation, storage, and injection; and affordability with long-lasting effects.

The first injectable fillers were derivatives of bovine collagen. Zyderm 1 and 2 (Inamed Corporation) were approved by the US Food and Drug Administration (FDA) in the 1980s for correction of contour deformities and acne scars.[1,2] However, the popularity of bovine collagen fillers has decreased because of the limited duration of results (2–3 months), manufacturing cost, and risk for hypersensitivity.[3] Although collagen fillers are no longer available in the United States, all other temporary fillers often are compared to them.

The shift from protein-derived filler materials to synthetic extracellular matrix materials (ie, HA) was a major advancement in soft tissue augmentation. Restylane (Medicis Aesthetics, Inc), an HA gel that was approved in 2003 for mid to deep dermal implantation for correction of moderate to severe facial wrinkles and folds, such as nasolabial folds, is produced by fermentation in cultures of equine streptococci and stabilized by cross-links of glycosaminoglycan chains.[1,4,5] It is a natural, rapidly degraded polysaccharide of the skin with low immunogenic potential. Processing HA to a less water-soluble hydrogel leads to longer retention times of 6 to 9 months. Restylane Fine Lines, which currently is not available in the United States, has a higher concentration of gel particles per milliliter to target thin superficial wrinkles; Perlane (Medicis Aesthetics, Inc) has the lowest concentration and is indicated for implantation into the deep dermis to superficial subcutis for the correction of

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moderate to severe facial folds and wrinkles, such as nasolabial folds.[1] Juvéderm (Allergan, Inc) has a higher concentration of HA and more cross-linking with increased longevity, reportedly lasting up to 12 months.[6] Most HA fillers differ in particle size, concentration, solubility, and gel hardness, which can influence the ease of injection, depth of implantation, longevity of effects, and local reactions. Hyaluronic acid has become the most widely used soft tissue implant, as it has an excellent safety profile, does not require skin testing prior to injection, and retains its effects longer than collagen.[2,7,8] Overtreatment can be easily corrected with hyaluronidase.[9] Common side effects include bruising, swelling, and pain, but the risk for hypersensitivity reactions is minimal.[10,11]

Alloplastic fillers that include both resorbable and nonresorbable components have been developed to improve product longevity. Radiesse (Merz Aesthetics, Inc) is a mixture of a glycerin-based aqueous gel and spherical microparticles of synthetic CaHA.[4] The FDA approved Radiesse in 2006 for subdermal implantation to correct moderate to severe facial wrinkles and folds, such as nasolabial folds. Theoretically, CaHA, a natural mineral in the body, should last for years with low solubility and minimal immunogenicity. Calcium hydroxylapatite has been shown to produce greater improvement and longer-lasting results than HA.[12] Because clumping or foreign body reactions may be seen if the product is injected too superficially or used in hyperdynamic areas, CaHA mostly is used for deep facial contouring and avoided in lip augmentation.[1] Sculptra Aesthetic (sanofi-aventis US LLC) is a biocompatible and biodegradable synthetic polymer of PLLA, an α-hydroxy acid manufactured from a resorbable plastic material.[13] Sculptra is hydrophilic and postimplantation hydrolysis leads to slow resorption by macrophage digestion. The FDA first approved Sculptra in 2004 for the treatment of human immunodeficiency virus–associated lipoatrophy and later approved Sculptra Aesthetic in 2009 for shallow to deep nasolabial fold contour deficiencies and other facial wrinkles, though the product commonly is used off label for volume enhancement in deeper areas.[14-18] Sculptra should be placed subdermally and has been found to provide clinical improvement for up to 2 years.[19-21]

Other filler materials also have been employed for soft tissue augmentation but are used less frequently. Allogeneic collagen-based fillers that are cultured from a single cell line of human dermal fibroblasts promise a decreased risk for immunogenicity compared to xenogeneic fillers.[1] Autologous fat transfer also is a promising option that decreases the risk for immune-mediated reactions; however, its highly unpredictable longevity and complicated harvesting process with the need for frequent injections make it clinically less desirable.[22,23] Permanent fillers such as silicone or polymethyl methacrylate guarantee long-lasting effects but also may cause longer-lasting complications that are more difficult to treat as well as aesthetic dissatisfaction that is not easily corrected.[24]

PATIENT SELECTION

During the initial consultation, baseline asymmetry, subjective defects, and realistic expectations should be discussed with the patient. Before and after photographs are strongly recommended. Additional factors that are important to consider during patient consultations include skin type, treatment location, desired effect, cost, duration of results, and comprehensive medical history. Choosing a filler is a multifactorial process. Injection depth and method, combination of different products, and appropriate volume are important in achieving optimal outcomes.[9]

A careful patient selection process will determine if the patient is not an ideal candidate for soft tissue augmentation with injectable fillers. Contraindications include prior allergy to the filler material or its constituents (eg, lidocaine). A thorough medical history is necessary to screen for keloids, bleeding disorders, or granulomatous diseases such as sarcoidosis. Preexisting lesions in the treatment area such as rashes, herpetic ulcerations, or impetigo may postpone the procedure. Cost is still a rate-limiting factor for many patients. For optimal results, many patients require treatment with 3 to 4 syringes of product but opt to purchase only 1. For the physician, trying to stretch 1 syringe over several areas rather than correcting 1 area well can result in suboptimal results and disappointed patients.[25]

The expected level of improvement and longevity also need to be discussed with the patient during the initial consultation. The duration of results for most filler materials is 6 to 12 months; however, this time frame does not equate to full correction but rather 1 degree of improvement on the wrinkle assessment scale after gradual volume diminishment. Experts have suggested a longer 18-month improvement with repeat treatment at a closer interval such as 4 months after initial injection.[26]

INJECTION TECHNIQUE

Sterilization is critical to prevent contamination during the initial handling, mixing, and injecting of the filler. Cleansing the skin with alcohol and changing gloves after intraoral manipulation also should be considered.[27] Although chlorhexidine has antibacterial effects, it should not be used in the periorbital region because of the risk for keratitis. Topical anesthetics, nerve blocks, or a combination of both also may be used. Concomitant injection

of local anesthetic and fillers also has been described, with many products now premixed.[28] Radiesse is the only filler that is FDA approved to be "swished" with lidocaine. It is recommended that physicians use the smallest needle possible, depending on the viscosity of the filler, to reduce pain, tissue trauma, risk for infection, and clumping.

Injection depth can be visually determined: the gray of a 26-gauge needle can be seen with intradermal injection and the shape of the needle can be seen with superficial subdermal injection.[29] Various injection methods have been described, but aesthetic results and longevity have not been compared in clinical trials. Linear threading is described as the deposition of material as the needle is withdrawn (retrograde) or advanced (anterograde). Anterograde injection is believed to be less painful and to cause less bruising; retrograde injection is believed to reduce adjacent tissue trauma, as it does not create additional tracks, which minimizes the risk for intravascular injection. The fanning technique involves placing multiple threads in different directions without withdrawing the needle from the original insertion site. Cross-hatching involves linear injections in a gridlike pattern to cover large areas. The serial puncture technique refers to the deposition of small droplets of filler administered at multiple injection sites. Ideal results for each technique may be dependent on the treatment location.[30] The only filler currently approved for use in the lips is Restylane. No product is approved for cheek augmentation, aside from human immunodeficiency virus–associated lipodystrophy; however, advanced and experienced practitioners regularly use fillers for off-label applications. Dilution of filler substances can decrease the viscosity of the product and increase the size of the treated area. Injection techniques that increase the dissection of the subepidermal plane (eg, fanlike needle use, rapid injection, rapid flow rates, higher volumes) have been known to increase local AEs. Injection techniques that increase epidermal damage or subcutaneous exposure (eg, multiple punctures, deep subcutaneous injection) seem to have no effect on AEs.[31]

PERIORBITAL IMPLANTATION

Botulinum toxin is a mainstay of soft tissue augmentation in the periorbital region. More recently, the addition of HA and other fillers have expanded the available options for treatment in this area.[32,33] A prospective randomized study of botulinum toxin used with HA filler for the treatment of glabellar rhytides improved outcomes, nearly doubling the median duration of response compared to filler alone.[34] Pretreatment of glabellar rhytides with botulinum toxin may obviate or decrease the need for filler. If resting lines are still present, techniques such as retrograde linear threading or deposition of small superficial aliquots via the serial puncture method are used to avoid intravascular injection. Avoiding stiffer products and large volumes of filler also can minimize vascular compromise and skin necrosis.[35] The hyperdynamic periorbital areas should be treated with softer products, as stiffer materials may bead when compressed by facial muscles. Treatment of the glabella and medial frontalis muscle with neurotoxins produces a lateral brow-lifting effect, which may lead to lateral forehead rhytides from compensatory muscle hypertrophy. One of the authors (M.P.L.) reports excellent results correcting this effect by elevating the lateral brow with filler.

A similar approach to the treatment of the glabella may be used for the crow's-feet and forehead. Periorbital lines of the inferolateral aspect are only partially treatable with neurotoxins; injection is limited in the inferior zygomatic area because of the potential for flattening of the lateral malar cheek and the risk for ptosis of the upper lip.[36] Small volumes of filler with appropriate physical properties administered using a slow injection technique are especially crucial because of the thin skin and rich subdermal vascular plexus in these locations.

The depression between the eyelid and the cheek, known as the tear trough (also referred to as the infraorbital hollow or nasojugal groove), can be treated with HA. This area is more easily assessed when the patient is seated, and marking the treatment sites is recommended to avoid overtreatment and asymmetry. The needle should be inserted just inferior to the orbital rim at the deepest depression in the medial aspect of the tear trough. Insertion until the needle touches bone is the desired endpoint to allow the filler to be placed below the suborbicularis oculi muscle plane. Placement of the filler above the periosteum minimizes visible nodules, but the infraorbital foramen should be avoided. A cannula also can be used at a more lateral insertion site with linear threads fanning the entire area where correction is needed. One of the authors (M.P.L.) recommends first treating the lateral area of the zygomatic arch to create a lifting effect, which decreases the need for treatment in the medial tear trough where large amounts of product can cause substantial AEs. Figures 1 and 2 demonstrate short-term results of treatment with HA filler in the tear trough area. Carruthers et al[35] described treating the malar contour first, followed by the orbital-malar groove and the nasojugal fold. To enhance the malar prominence, injections administered in multiple layers beneath the dermis and above the periosteum using a retrograde fanning technique also have been noted.[37] The lifting effect that treatment of this area provides may reduce the amount of filler needed in the surrounding areas, especially more

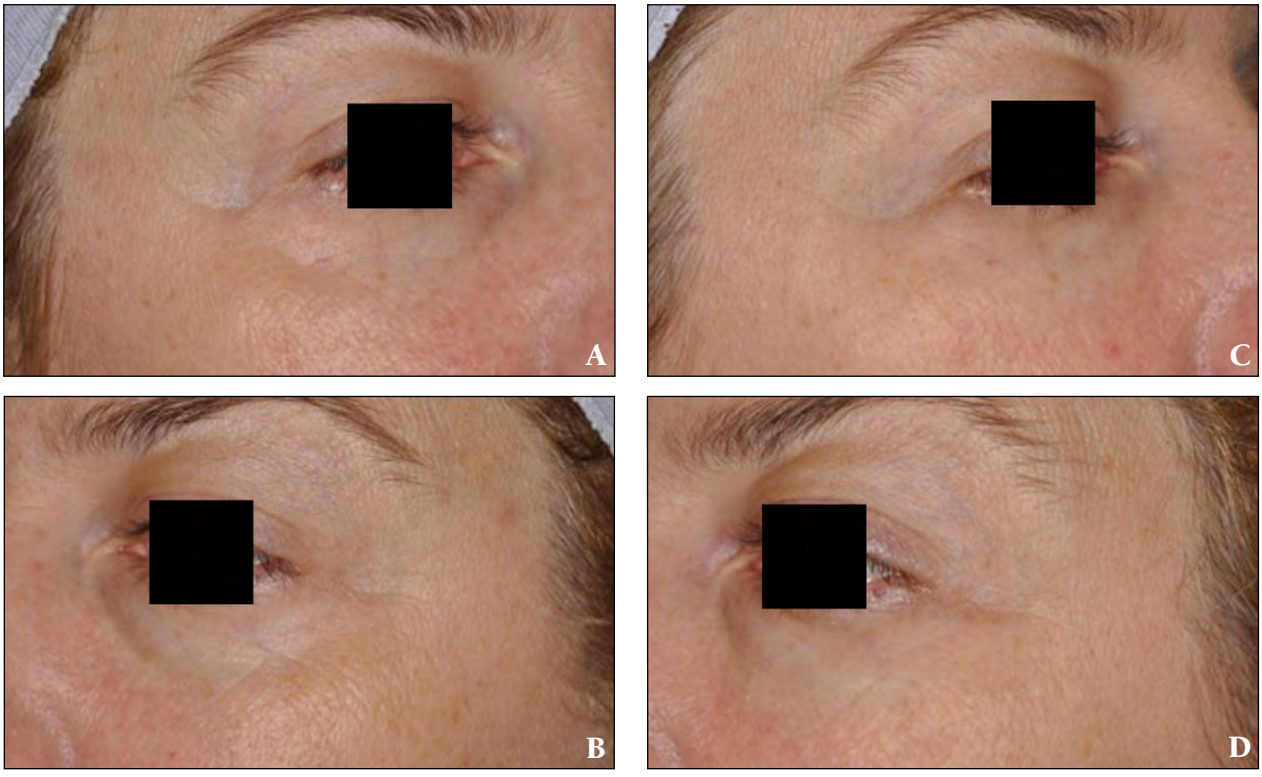

Figure 1. Patient before (A and B) and 6 months after tear trough injection with hyaluronic acid filler (C and D). Photographs courtesy of Mary P. Lupo, MD, New Orleans, Louisiana.

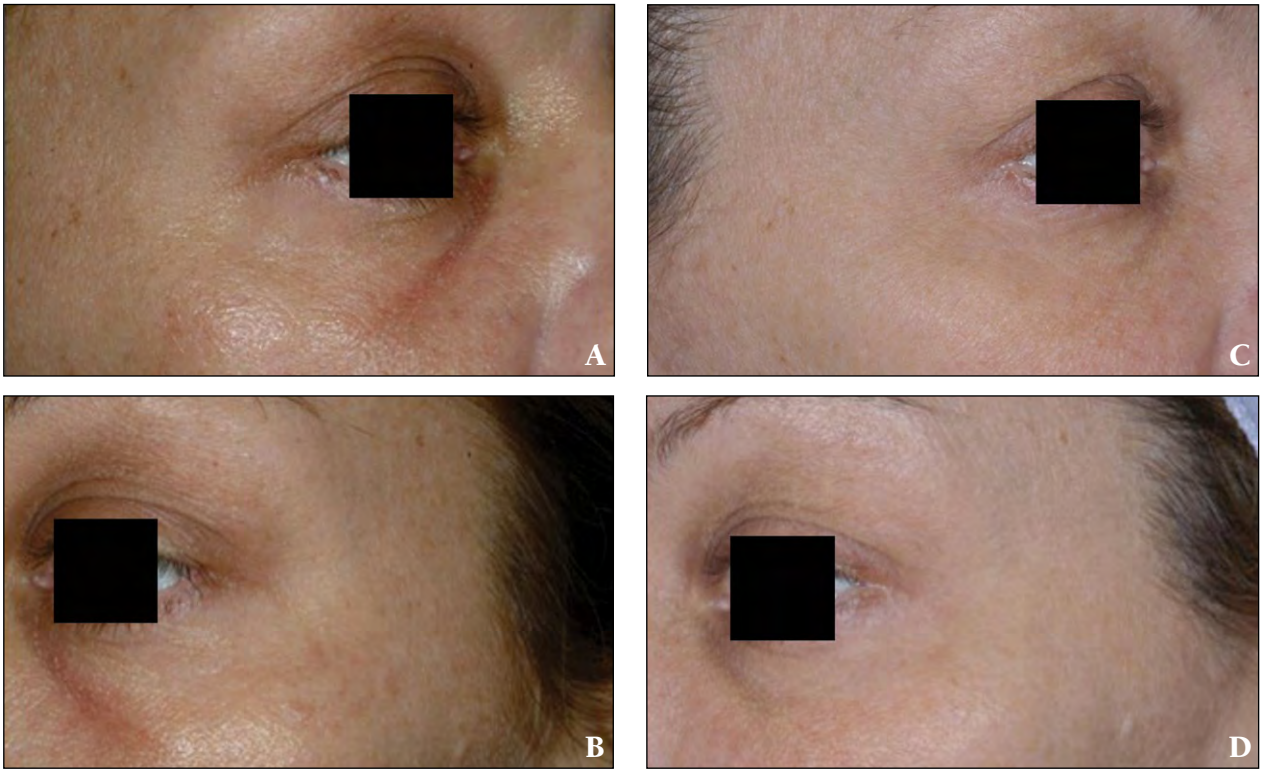

Figure 2. Patient before (A and B) and 6 months after tear trough injection with hyaluronic acid filler (C and D). Photographs courtesy of Mary P. Lupo, MD, New Orleans, Louisiana.

caudal areas such as the nasolabial folds. Calcium hydroxylapatite and PLLA also can be used off label for volume replacement and facial contouring in these areas because injection often is in deeper planes. Conservative amounts of filler are recommended, with follow-up within 2 to 4 weeks for touch-ups to avoid overcorrection in 1 visit.[33] When treating larger areas and injecting at deeper levels, cannulas are preferred.[38] In a double-blind, randomized, controlled trial comparing the safety and efficacy of a 21-gauge metallic cannula to a standard 30-gauge needle, the cannula-treated side showed reduced instances of erythema, edema, hematoma, and pain.[39] Fewer injection sites also decrease the need for local nerve blocks or large amounts of topical anesthetics. A small amount of intradermal local anesthetic can be used prior to making the insertion site for the cannula with a needle with a larger bore and often is all that is required.

POSSIBLE AEs

Adverse events associated with injectable fillers usually are self-limited, and satisfaction rates are high. Frequent complications in the periorbital area include bruising, contour irregularities, and color change. Bruising is most likely to occur if the needle passes through the orbicularis muscle. Avoiding obvious blood vessels, using a vasoconstrictive agent, discontinuing blood thinning agents, and applying ice after the procedure can be helpful to minimize bruising. Retrograde threading or use of a blunt cannula also may prevent vascular compromise.[38]

Contour irregularities can be corrected at follow-up. Hyaluronidase can dissolve HA granulomas or superficial placement resulting in a blue-gray cast. Effects have been noted immediately after injection of 30 to 40 U per 0.5-cm nodule. Jones et al[40] noted that larger volumes of hyaluronidase were required to correct results from Juvéderm versus Restylane. Brand name products are recommended to decrease the potential for formula variation. Lumpiness and foreign body granulomas are associated more often with semipermanent fillers.[21,41] Subcutaneous nodules may require excision.[42] Sculptra's original instructions for dilution with 2 cc of bacteriostatic water and a 2-hour reconstitution time[43] initially were associated with an increased risk for granuloma formation; however, one author's experience (M.P.L.) has shown that the new convention of care that calls for dilution of Sculptra with 6 to 9 cc of bacteriostatic water and longer reconstitution times of more than 24 hours (off label) results in a decreased incidence of AEs. Color change often is described as appearing blue or gray and is more common in fair-skinned patients. Baseline hyperpigmentation should be documented, as some patients note worsening of dark circles under the eyes after filler injections.[44]

Development of malar edema is a rare complication that often lasts for many weeks and is variably responsive to hyaluronidase. It is noted more commonly in older patients with thinner skin who have a tendency for edema even prior to treatment. The reason is unclear but seems to be exacerbated by the hydrophilic properties of HA. More severe complications from intravascular injection with local occlusion or distant embolization include skin necrosis and possible vision impairment.[44] Withdrawing the plunger slightly prior to injection to ensure it is not within a vessel and using conservative amounts of filler reduce these risks.

CONCLUSION

Soft tissue augmentation with temporary fillers continues to increase in popularity. Major advancements have been made over the last few decades in the transition from bovine collagen to nonanimal HA fillers, with decreases in hypersensitivity reactions and increased longevity. Semipermanent fillers such as CaHA and PLLA have longer-lasting results but often are associated with an increased risk for AEs, including granuloma formation. Hyaluronic acid still remains the most widely used filler. Traditionally, injectable fillers have been used to reduce the appearance of skin folds and wrinkles, such as the nasolabial folds, as well as for lip augmentation. More recently, the use of soft tissue fillers has expanded from use in the lower face to the mid and upper face. In addition to the correction of glabellar wrinkles and crow's-feet, volume replacement and contour reshaping of the malar prominence and tear trough areas are now performed to create a more natural, youthful appearance. Various site-specific techniques are now being described in clinical trials, such as serial puncture in the glabella and supraperiosteal retrograde fanning in the tear troughs.[30,31] Controlled trials currently compare longevity and AEs of different filler materials,[2,6,10,12] but further studies comparing efficacy and results of different injection methods are needed. Overall, patient satisfaction generally is high and reported AEs are low. Off-label uses and new approaches to reduce the signs of aging continue to increase.

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