

Hyaluronic Acid Fillers in Facial Rejuvenation

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Nonsurgical procedures have become very popular for the rejuvenation of the aging face. Trends now are for less invasive procedures as well as for more preventative intervention to slow the damage from ultraviolet light and environmental factors, as well as from intrinsic aging. The goal of these procedures is to eliminate or delay the need for corrective surgery. The regular use of sunscreens; retinoids and improved cosmeceuticals; injectable neurotoxins; soft-tissue augmentation products; and minimally invasive laser, light, and radio-frequency treatments are decreasing and delaying need for invasive procedures. Injectable fillers entered mainstream cosmetic medicine with the development of bovine collagen injections in the 1980s. The availability of improved fillers that are less allergenic and longer lasting has resulted in a renaissance in filler techniques. No single filler has proven to be more popular than the category of hyaluronic acids (HA). This article will review the use of the hyaluronic acid fillers that are currently approved for use by the Federal Drug Administration in the United States and describe the significant differences between them to assist the practicing cosmetic physician in choosing and using this category of dermal filler.

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Today's cosmetic dermatologist is *the* specialist in nonsurgical rejuvenation of the aging face. Many tools and techniques are available to achieve this goal. Although the process of skin aging is complex and beyond the scope of this review, it is sufficient to state that correction of aging skin requires a global approach that addresses the sequelae of both intrinsic (chronological) as well as extrinsic (primarily solar-induced) aging, using combination protocols.¹

Cosmeceuticals have been developed that mitigate the signs of photoaging, and this topic is explored more extensively in this issue. Topical antioxidants are available that reduce free radical damage to the skin, stimulate collagen production, improve color and texture, and decrease fine lines. Additional ingredients may improve the barrier function of dehydrated, aging skin.²⁻⁴ It must always be remembered, however, that topical retinoids remain the gold standard in treating the visible signs of photoaging.⁵ Less-aggressive techniques to enhance the appearance of the skin include light chemical peels and particle resurfacing also known as "microdermabrasion." These are popular because they are "no downtime" procedures.^{6,7} Injectable neurotoxins such as botulinum toxin type A dramatically improve wrinkles that are the result of facial musculature movement.⁸ La-

ser, pulsed noncoherent light, and other energy sources such as radiofrequency energy improve skin coloration, thicken dermal architecture, and tighten lax skin without cutting.^{9,10} The final, and perhaps most popular, tool to add to combination protocols for noninvasive facial rejuvenation is dermal fillers.

Filler History

For more than 20 years, the only fillers approved by the Food and Drug Administration (FDA) in the United States were forms of bovine collagen. Available in 3 forms, Zyderm I, Zyderm II, and the more highly cross linked Zyplast, they were our only realistic options for most patients wanting soft tissue augmentation. Allergic reaction rates were approximately 3% before the adoption of 2 pretreatment skin tests.^{11,12} The availability of human-derived CosmoDerm^R and CosmoPlast^R in March, 2003 obviated the need for skin testing and was a major breakthrough in esthetic dermatology. Patients could be treated at the time of consultation. Still, there was a need for fillers with greater longevity and more volume restoration than these collagen based products provided. Hyaluronic acid fillers, widely available outside of the United States, were the obvious choice to fill this need.

The visible signs of facial aging partially result from changes in dentition and bony architecture. Facial fat loss and diminished dermal thickness from extrinsic (primarily photodamage) and intrinsic (the result of time and genetics) aging also contribute to the visible signs of aging. The addi-

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Figure 1 A 28-year-old woman before restylane injection.



Figure 2 The same woman 1 week after injection into nasolabial fold.

tional loss of the collagen and the glycosaminoglycans (GAG) support structures that provide turgidity and support to the skin adds further to the appearance of aging. This loss of dermal and subcutaneous support results in folds and hollows that age the face. Filling concavities of the face with fillers such as the hyaluronic acids, restores a more youthful appearance without the need for cutting and redraping as is done with a face lift.

Science of Hyaluronic

Hyaluronic acid (HA) is one of the most prevalent glycosaminoglycans in the dermis, so its utility as a dermal filler is obvious. Because HA is not species specific, there is theoretically no need for skin testing for allergenicity. HA is a polysaccharide composed of repeating units of D-glucuronic acid



Figure 3 A 52-year-old African-American woman before injection.



Figure 4 The same woman after Hylaform Plus and Restylane into nasolabial and marionette folds.



Figure 5 A 24-year-old woman.

and N-acetyl-glucosamine. It is found in all tissues of vertebrates and is very prevalent in human skin. It has been demonstrated to be decreased in intrinsically aged skin and to be altered in photoaged skin.^{13,14} HA is highly hydrophilic, binding much more than its weight in water. To be practical as a filler, however, crosslinking of the polysaccharide chains is necessary to slow degradation. Hyaluronic acid fillers are mainly used in the nasolabial fold, which was the site of original testing for FDA approval (Figs. 1 and 2). They are also commonly used “off label” in many other areas, including the lips and marionette folds (Figs. 3, 4, 5, and 6). Facial reshaping can be achieved by injecting HA into the cheek prominence and lateral brow. Advanced injectors place HA in the glabella crease, mental crease as well as the ocular sulcus and tear trough region.¹⁵

Injection technique varies among injectors, with antegrade and retrograde threading as well as serial puncture being used. When injecting HA, it is important for the tip of the needle to be in the mid to deep dermis to avoid bluish discoloration or lumping that may be seen with superficial injections. Placement of HA too deeply in the dermis will compromise the duration and extent of the correction obtained. Before injection near the orbital rim, it is important to aspirate the syringe to avoid inadvertent intravascular injection in this highly vascular region.

At the present time, there are 4 HA fillers approved for use in the United States by the FDA. Restylane[®] (Medicis Aesthetics Inc., Scottsdale, AZ), a nonanimal stabilized hyaluronic acid (NASHA) of medium viscosity for mid- to deep dermal correction, was the first approved in December 2003, followed by the approval of Hylaform[®], which is derived from rooster combs, in April 2004. Hylaform Plus[®], formulated for deeper dermal injection was approved in October 2004 and Captique[™] followed in December 2004. A summary of the difference of these products is found in Table 1. Differences in molecular weight, particle size, and proprietary differences in crosslinking have resulted in theoretical variations in product behavior and duration. Some published experts believe that Hylaform has characteristics that result in decreased swelling and bruising.¹⁶ There is widespread anecdotal reporting of greater duration with Restylane. A recent



Figure 6 The same woman immediately after an injection of Hylaform into the lips.

published report documented higher efficacy and patient satisfaction with Restylane over Hylaform after 12 weeks.¹⁷ Another study showed more durable correction at six months with Restylane Perlane (a more viscous NASHA not currently available in the United States) over Hylaform.¹⁸ I have found benefit from layering medium-viscosity products such as Restylane in the mid dermis with larger particle Hylaform Plus in the deep dermis for those with deep nasolabial folds. Hylaform can replace Cosmoderm in the higher dermis if injected with a fine gauge needle to fill more etched and fine skin lines.

Complications

There is no medical procedure totally devoid of risks. It is important to review all known potential side effects with the patient to obtain informed medical consent. Clinical trials have documented the overwhelming safety profile of all forms of HA.¹⁹ Transient and self-limiting redness and swelling are common following injections of HA and this is due to the hydrophilic nature of HA. For this reason, correction should never be greater than 100%. Pain associated with injection of HA may be managed by the use of both topical and injected anesthetic agents. This is especially important for lip injections where a superficial gingival block in the sulcus of the oral cavity provides one hour of anesthesia without the extended numbness and occasional morbidity seen with a nerve block. Despite adequate anesthesia, patients can expect tenderness for 1 to 2 days after injection. Rarely do patients require treatment with analgesics.

Nodule formation is possible after injection of any filler. Typically, this results from intermittent over-injection and the rate of nodule formation decreases with injector experience. If nodule formation is noted, gentle massage may decrease the appearance of the nodule but care should be taken to avoid over vigorous massage which will increase bruising. Bruising is, by far, the most common complication that is disturbing to patients (Fig. 7). Redness, swelling, and tenderness usually fade after 24 hours, but bruising may persist for days and sometimes up to 1 week. One possible reason that

Table 1 Product Differences

	Restylane	Hylaform	Hylaform Plus	Captique
Source	Bacterial	Avian	Avian	Bacterial
Concentration	20 mg/ml	5.5 mg/ml	5.5 mg/ml	5.5 mg/ml
MW of raw HA	1.5–2 M	4–6 M	4–6 M	1.5–2 M
Median particle size	300 microns	500 microns	700 microns	500 microns
Polymer	Short chain, tight configuration	Long chain, loose configuration	Long chain, loose configuration	Short chain, tight configuration
Crosslink agent	BDDE	DVS	DVS	DVS

BDDE, 1,4-butandiol diglycidylether; DVS, divinyl sulfone.

HA causes more bruising is its structurally similar to heparin. Baumann has advocated the use of collagen injection along with the HA to reduce bruising.²⁰ She postulates that the lidocaine in the Cosmoderm or Cosmoplast has an antibruising benefit, but there have been no controlled studies to substantiate this hypothesis. Lidocaine is known to decrease the activation of eosinophils that may stimulate bruising.²¹ Reducing the number of needle sticks in a given treatment has decreased bruising in my practice and is one reason I recommend threading over serial puncture with HA fillers.

Finally, true allergic reactions to HA have been reported.^{22,23} Treatment with intralesional and topical corticosteroids as well as topical immune modulating agents have been tried with limited success.^{23,24} One of the unique benefits of utilizing HA fillers is the ability to correct lumps and even eliminate allergic responses by the injection of hyaluronidase to enzymatically degrade the HA filler quickly. Hyaluronidase injections are the treatment of choice to reverse allergic reactions.^{24,25}

The Future

It is reasonable for the practicing esthetic physician to expect additional fillers to be available in the US over the next several years. European and Canadian physicians have experience with other forms of Restylane such as Perlane for deep dermal and subcutaneous correction and Restylane Touch for papillary dermal correction of fine lines. A smaller particle form of Hylaform may come to the U.S. market as well. Another HA

filler, Juvederm, is widely available and popular outside the US and is being evaluated for FDA approval. Discussion of this product in this article is not appropriate since it is currently undergoing FDA evaluation, but experts report excellent cosmetic correction with natural softness combined with long duration.^{26,27}

What is clear is that worldwide usage and published reports confirm the efficacy and safety of hyaluronic acid fillers. Popularity of such fillers continues to increase as the aging population seeks options to correct the signs of aging without surgery. Fillers such as the hyaluronic acids are obviously one of the key components to the successful combination treatment of the aging face.

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Figure 7 A bruise is evident 3 days after restylane injection.

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