The Role of Hyaluronic Acid Fillers (Restylane) in Facial Cosmetic Surgery: Review and Technical Considerations

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Background: Bioengineered hyaluronic acid derivatives are currently available that provide for safe and effective soft-tissue augmentation in the comprehensive approach to nonsurgical facial rejuvenation. Current hyaluronic acid fillers do not require preinjection skin testing and produce reproducible, longer-lasting, nonpermanent results compared with other fillers, such as collagen.
Methods: A review of the authors' extensive experience at the University of Texas Southwestern Medical Center was conducted to formulate the salient requirements for successful utilization of hyaluronic acid fillers. Indications, technical refinements, and key components for optimized product administration categorized by anatomical location are described. The efficacy and longevity of results are also discussed.
Results: Bioengineered hyaluronic acid fillers allow for safe and effective augmentation of selected anatomical regions of the face, when properly administered. Combined treatment with botulinum toxin type A can enhance the effects and longevity by as much as 50 percent. Key components to optimal filler administration include proper anatomical evaluation, changing or combining various fillers based on particle size, altering the depth of injection, using different injection techniques, and coadministration of botulinum toxin type A when indicated. Concomitant administration of hyaluronic acid fillers along with surgical methods of facial rejuvenation can serve as a powerful tool in maximizing a comprehensive treatment plan.
Conclusions: Current techniques in nonsurgical facial rejuvenation and shaping with hyaluronic acid fillers are safe, effective, and long-lasting. Combination regimens that include surgical facial rejuvenation techniques and/or coadministration of botulinum toxin type A further optimize results, leading to greater patient satisfaction. (*Plast. Reconstr. Surg.* 120 (Suppl.): 41S, 2007.)

Soft-tissue augmentation with the various soft-tissue filler materials has become one of the most popular aesthetic procedures available to patients who desire nonsurgical facial rejuvenation. The plethora of soft-tissue fillers currently available in the United States today also serves as a powerful adjunct to surgical techniques in facial rejuvenation and facial shaping. The 2003 data from the American Society of Plastic Surgeons demonstrated a 150 percent increase from 2002 in the use of soft-tissue fillers, with 744,283 procedures performed in this nonsurgical category.[1,2] Soft-tissue fillers are particularly attractive to younger, middle-aged patients who display minimal to moderate signs of facial aging and who want minimal downtime.

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FDA Status and Approved Uses: Restylane is FDA approved as an injectable gel to treat facial wrinkles. Juvéderm is FDA approved. The three product formulations include Juvéderm 24 HV, a highly cross-linked formulation for more versatility in contouring and volumizing of facial wrinkles and folds; Juvéderm 30 HV dermal filler, a more highly cross-linked

Continued

As the search for an ideal filler material continues, hyaluronic acid derivatives have gained popularity among aesthetic surgeons because of their numerous advantages. An ideal filler material is one that is biocompatible, nonantigenic, nontoxic, easy to use, long-lasting (yet nonpermanent), inexpensive, and reversible. It should demonstrate a high safety profile and produce a predictable result with minimal downtime.

Many of the new fillers available for use in the United States are longer-lasting and have shifted the paradigm between permanent and nonpermanent fillers. Use of permanent or "more permanent" fillers allows less room for error and can produce irreversible changes in facial shape that may not retain the aesthetic changes as the patient ages. With the introduction of hyaluronic acid derivatives for use in soft-tissue augmentation, a safer, longer-lasting, and yet temporary alternative has been made available.

WHAT IS HYALURONIC ACID?

Hyaluronic acid is common among many organisms and is present in connective tissues of skin, cartilage, bone, and synovial fluid. Hyaluronic acid is unique in that it is natively present in the intracellular matrix of the dermis and identical in form in all mammalian species.[3,4] In human skin, it aids in bulk, lubrication, and shock absorption. Its viscoelastic properties and role in cell membrane protection and stabilization make it a natural choice for dermal soft-tissue augmentation. The amount of hyaluronic acid residing in native tissue decreases with age, leading to reduced dermal hydration and increased folding.[5,6]

Hyaluronic acid is a glycosaminoglycan biopolymer of alternating D-glucuronic acid and N-acetyl-D-glucosamine monosaccharide residues cross-linked into long, repeated, unbranched polyanionic chains. The repeating chains are hydrated and coil upon themselves, providing the substance with elasticity and viscosity. Hyaluronic acid acts by binding water molecules, which leads to increased skin hydration and turgor. Its hydrophilic properties help the product maintain its volume and viscoelasticity when it is injected.

Exogenous hyaluronic acid is rapidly eliminated by lymphatics and degraded in the liver to carbon dioxide and water.[5] Without cross-linking, the tissue half-life is only 1 to 2 days. Manufacturers, therefore, have had to modify the physical and chemical properties to allow long-lasting results.

The goal of bioengineered hyaluronic acid is to improve its stabilization via increased tissue residency, viscosity, and elasticity while preserving its innate biocompatibility. The bioengineered hyaluronic acid derivative is chemically cross-linked, which alters its solubility and rheological profile so that it becomes a more viscous, water-insoluble gel. This process has dramatically improved its stability when it is injected into tissue. The hyaluronic acid gel properties are, therefore, controlled by varying the molecular weight, concentration, and degree of cross-linking. This process helps retain the biological compatibility of the native polymer, slow its dissolution rate, and increase its residence time when it is injected into dermis.[7–12]

Hyaluronic acid derivatives first received Food and Drug Administration approval in the United States for soft-tissue augmentation in December of 2003 with the introduction of Restylane (Medicis Aesthetics, Inc., Scottsdale, Ariz.) followed by Hylaform (Inamed, Santa Barbara, Calif.) in April of 2004, Hylaform Plus in October of 2004, and Captique (Allergan, Santa Barbara, Calif.) in December of 2004.[13–15] The majority of the long-term experience with these filler products can be found in both the European and Canadian literature, with up to 9 years of experience in more than one million patients. The hyaluronic acid derivatives available in these countries include Hylaform Gel, Hylan Rofilan Gel, Achyal, Restylane, Restylane Fine Lines, and Perlane.[16] These various hyaluronic acid derivatives differ in particle size, molecular weight, and degree of cross-linking, making each optimal for injection into specific dermal layers and facial regions (Table 1).

For example, Restylane Fine Lines is a lower-density, less viscous filler that is indicated for the more superficial dermis (dermoepidermal junction), whereas Restylane is composed of medium-density particles, more viscous, and better suited for augmentation of the mid-dermis. Perlane is a high-density, longer-lasting hyaluronic acid filler

robust formulation for volumizing and correction of deeper folds and wrinkles; and Juvéderm 30, a highly cross-linked formulation for subtle correction of facial wrinkles and folds. Captique is approved for injection into the mid- to deep dermis for correction of moderate to severe facial wrinkles. Hylaform is approved for injection into the mid- to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds).

Table 1. Characteristics of Various Hyaluronic Acid Fillers

	Restylane	Hylaform	Hylaform Plus	Captique
Cross-linking agent	BDDE	DVS	DVS	DVS
HA concentration	20 mg/ml	5.5 mg/ml	5.5 mg/ml	5.5 mg/ml
Particle size	250 μm	500 μm	750 μm	500 μm

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

that is very useful for deep dermal injection. Perlane is currently the largest hyaluronic acid compound available. Perlane is an effective, long-lasting filler indicated for augmentation of the deeper dermal level. However, thicker hyaluronic acid fillers (i.e., larger particle size) can be less forgiving in more superficial dermal layers and can produce lumpiness and more erythema if caution is not used.

COMMERCIALLY AVAILABLE HYALURONIC ACID PRODUCTS (UNITED STATES)

Restylane

Restylane is a partially cross-linked hyaluronic acid derivative obtained from a bacterial (*Streptococcus*) fermentation process that forms a viscoelastic, transparent gel. Because it is a non–animal-derived compound, there is no risk of transmitting diseases and minimal risk of allergic reactions, so the need for preinjection skin testing is eliminated. As with other bioengineered hyaluronic acid derivatives, Restylane binds water with great affinity and can maintain its bulk as it undergoes "isovolemic degradation." This stability is provided by the high degree of cross-linking, which allows for its long-lasting effect (up to 4 to 6 months, depending on the location and injection technique).[17] Restylane is indicated for mid- to deep dermal implantation for moderate to severe facial wrinkles and folds/nasolabial folds.[14,17] Restylane is provided in 0.4-ml and 1.0-ml preloaded, 30-gauge, 1.5-inch-long needle syringes containing 20 mg/ml of stabilized hyaluronic acid.[18,19] The product syringes have a shelf life of 1.5 years.

Hylaform/Hylaform Plus

Hylaform and Hylaform Plus, both hyaluronic acids derived from avian proteins, were approved by the Food and Drug Administration in April and October of 2004, respectively.[15] These products are indicated for injection into the mid- to deep dermis for correction of moderate to severe facial wrinkles and folds. Both products are supplied in individual treatment syringes, with 30-gauge needles packaged for single-patient use and ready for injection. Each syringe contains a solution of hylan B gel (5.5 mg/ml), sodium chloride (8.5 mg/ml), and water. Hylaform Plus has a larger particle size compared with Hylaform.[15,20–22] As with other hyaluronic acid derivatives, no skin testing is required.

Juvéderm

Juvéderm (Allergan, Inc., Irvine, Calif.) was approved by the Food and Drug Administration in June of 2006 for use as a dermal filler. The makers of Juvéderm consider it to be "next generation" hyaluronic acid–based dermal filler.[22] It possesses all the benefits of a hyaluronic acid–based filler and reportedly comes in a smooth gel form that is different from other hyaluronic acid fillers that use particle suspension technology.[22] In addition, the manufacturer states that it contains the highest concentration of nonanimal and cross-linked hyaluronic acid currently available.[22] There are three formulations available: Juvéderm 24 HV, a highly cross-linked formulation; Juvéderm 30 HV dermal filler, a more highly cross-linked robust formulation intended for deeper filling; and Juvéderm 30, for more shallow and superficial dermal augmentation.

Captique

Captique is a newer hyaluronic acid derivative, manufactured and packaged in the same manner as Hylaform. It was approved by the Food and Drug Administration in December of 2004 based largely on the approval of Hylaform. Captique differs from Hylaform in that it is derived from a bacterial source rather than an avian source. Captique is indicated for injection into the mid- to deep dermis for correction of moderate to severe facial wrinkles.[13,22]

EFFICACY

The efficacy of hyaluronic acid fillers has been demonstrated in numerous clinical trials. Olenius[16] found in his series of 100 patients treated with Restylane that 60 percent of the effect was present at the 12-month follow-up. In a prospective, randomized, controlled study using a non–animal-sourced hyaluronic acid [or NASHA (Restylane)] in combination with botulinum toxin type A (Botox; Allergan

Irvine, Calif.), Carruthers and Carruthers[23] demonstrated an improved and longer-lasting aesthetic response for glabellar rhytides when Restylane was used in combination with Botox. At a follow-up of 16 weeks, 83 percent of the Restylane group, compared with 95 percent of the Botox/Restylane group, had aesthetic improvement.[23] This finding may be explained by the reduction in dynamic muscle action that could reduce filler deformation within the dermis. In addition, the subjects in the study commented on more "instantaneous" results when Restylane was added to Botox treatment for severe glabellar folds.[23]

In a pivotal one-to-one randomized, double-blind, multicenter trial, Narins et al.[17] compared the efficacy of Zyplast [bovine collagen (Allergan, Santa Barbara, Calif.)] to that of Restylane in the treatment of nasolabial folds. Using a Wrinkle Severity Rating Scale and a Global Aesthetic Improvement Scale, the authors found that Restylane required less volume and fewer treatments to achieve an "optimal cosmetic result," as evaluated by blinded investigators.[16] In addition, both Restylane and Zyplast demonstrated a similar safety profile.[16]

The pivotal trial for Hylaform compared the safety and efficacy of Hylaform viscoelastic gel with those of Zyplast for the correction of nasolabial folds in a prospective, multicenter, randomized, double-blind, parallel-group study conducted during an initial 12-week treatment phase.[15,20] Hylaform gel was found by an independent review of photographs to be equivalent to Zyplast (control filler) in the correction of nasolabial folds.[20] As of this writing, there have been no clinical trials involving the use of Captique; Food and Drug Administration approval of this product was based on trials involving other hyaluronic acid fillers.[13]

LONGEVITY

One significant advantage of hyaluronic fillers over more traditional nonpermanent fillers, such as fat and collagen, is their increased tissue longevity (Table 2). In our clinical experience, the purported longevity of 6 months has not been seen in all areas of injection. In the tear trough, malar, and glabellar regions, the longest longevity we have seen has been approximately 6 months. This has been enhanced to as long as 9 months with concomitant Botox treatment in the glabellar and forehead regions. In the nasolabial fold, adjunctive injections are usually necessary within 4 to 6 months and are required less often as injection sessions proceed. A layering technique in this area can also prolong injection intervals. The shortest duration, of approximately 3 to 4 months, has been seen in the lip region in our patients, chiefly in long-lip patients with minimal initial bulk. Before injection, all patients are informed of the inherent variability in duration of effect; this is a critical part of the informed consent process. Reinjections (not including touch-ups) of specific areas are usually performed 4 to 6 months after the initial injection. In our experience, an additive effect is evident as the number of injections increases. Often, progressively less product volume is required with each subsequent injection.

Table 2. Longevity of Hyaluronic Acid

Treatment Area	Longevity
Lips	3–4 months
Nasolabial fold	4–6 months
Tear trough	>6 months
Glabellar and forehead region	6 months (up to 9 months with Botox*)
Oral commissures	3–4 months

*Efficacy is enhanced by up to 50 percent in the lip, glabellar, forehead, and oral commissure areas with coadministration of Botox.

INDICATIONS

With aging, the skin loses its viscoelasticity, which is maintained in part through the innate properties of hyaluronic acid. Volume loss, especially in the lips, nasolabial, and malar regions, is seen with advanced age. Useful, more objective methods of rating the severity of facial rhytides and the corrective results have been described by Fitzpatrick et al.,[24] Glogau,[25] and Lemperle et al.[26] Lemperle et al.[26] developed a 0- to 5-point rating scale to assess results after soft-tissue augmentation with fillers (Table 3).

Table 3. Classification of Facial Wrinkles*

Grade	Description	Areas Assessed
0	No wrinkles	Horizontal forehead lines
1	Just perceptible wrinkle	Glabellar frown lines
2	Shallow wrinkles	Periorbital lines
3	Moderately deep wrinkle	Preauricular lines
4	Deep wrinkle, well-defined edges	Cheek lines
5	Very deep wrinkle, redundant fold	Nasolabial folds Radial upper lip lines Radial lower lip lines Marionette lines Labiomental crease

*Adapted from Lemperle, G., Holmes, R. E., Cohen, S. R., and Lemperle, S. M. A classification of facial wrinkles. *Plast. Reconstr. Surg.* 108: 1735, 2001.

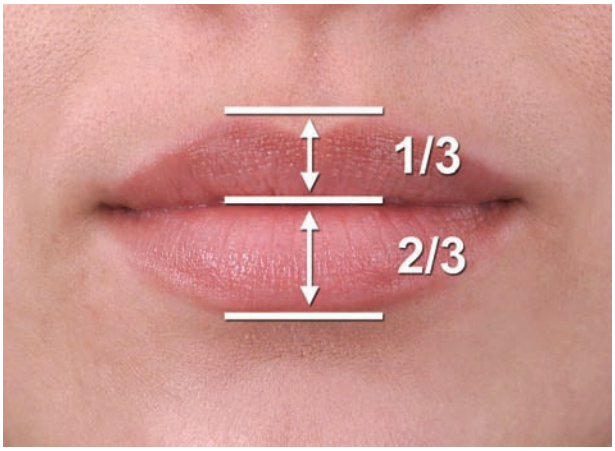

Fig. 1. Aesthetic upper-to-lower lip height balance. The upper lip is approximately one-third of the height and the lower lip is two-thirds of the total lip height. This corresponds to the relative volume differences between the upper and lower lips.

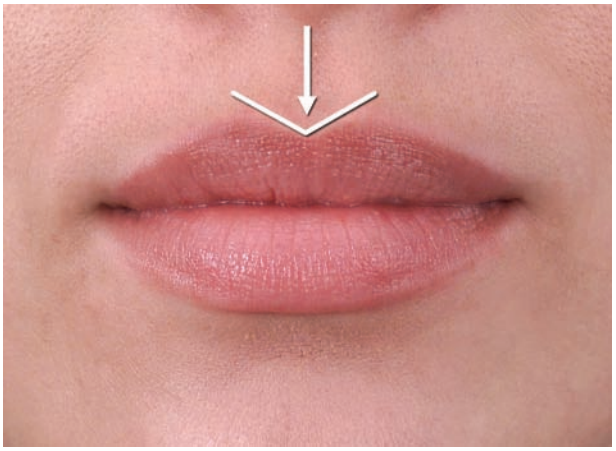

Fig. 2. The Cupid's bow is sharp and well defined in youthful lips.

The lips and perioral region are the central aesthetic component of the lower third of the face. Lips express emotion, sensuality, and vitality. In evaluating the aesthetic lip, it is critical to assess the surrounding soft tissues as well as the maxillofacial harmony (Fig. 1). Some of the characteristics of an aesthetic and youthful lip are listed in Table 4 and shown in Figures 1 through 5. With aging, the lips undergo changes in vermilion bulk (pout) and exposure (thin lips) that can be exaggerated by bony retrusion and changes in dentition (Fig. 4). Patients who require subtle refinements in lip fullness, projection, and degree of eversion are ideal candidates for augmentation with hyaluronic acid fillers (Fig. 5). In addition, marionette lines, the deep mental groove, and the anterior jowl line must also be evaluated and augmented when indicated, to optimize overall lip and perioral aesthetics.

With increasing nasolabial fold depths, the face appears older and lacking in midface support. Hyaluronic acid fillers are ideal for blunting prominent nasolabial folds. Malar atrophy, resulting from fat, muscle, and skeletal atrophy, and soft-tissue descent contribute to the aging appearance of the middle third of the face (Fig. 6). Combining both surgical and nonsurgical options to provide support and fullness to the midface can result in marked rejuvenation in this facial region. It is not uncommon to perform a face lift and inject hyaluronic acid filler into the lips, nasolabial folds, and malar or nasojugal areas. Hyaluronic acid aug-

Table 4. Comparative Features of the Youthful/Aesthetic Lip and the Aging Lip

Aesthetic Lip	Aging Lip
One-third upper to two-thirds lower lip height ratio	Upper and lower lips equal out, thin, and stretch out
Distinct Cupid's bow	Loss of Cupid's bow
Central fullness of the upper lip	Thin, uniform, contoured upper lip
Concave sloping of the upper and lower lips	Convex, ill-defined sloping projection from the nasal base and labiomental groove
Upper lip 1–2 mm anterior to the lower lip	Equalized projection of the lips
Vermilio-cutaneous borders thickened with a pout	Loss of vermilio-cutaneous pout
Philtral columns prominent and full	Philtral columns flattened
Commissures slightly upturned	Commissures downturned

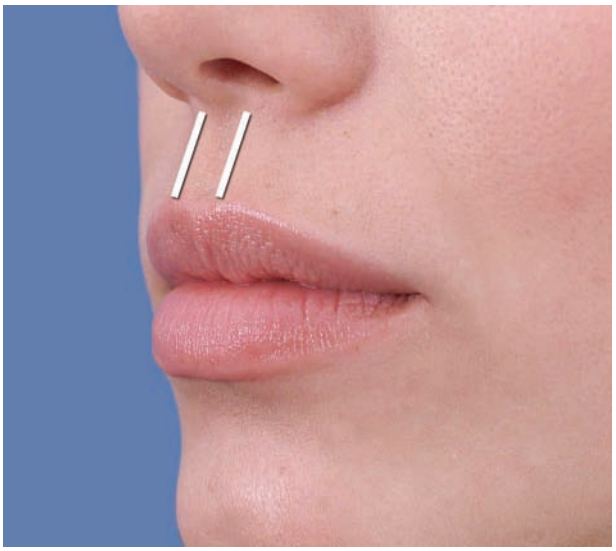

Fig. 3. Youthful lips have full philtral columns that add upper lip-to-nasal base fullness.

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