Treatment With Hyaluronic Acid Fillers

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Hyaluronic acid (HA) fillers are a mainstay of cosmetic dermatology. The following article reviews the properties of these fillers as well as current and future uses for the HAs. We also discuss potential complications associated with their use.

John Keats, the celebrated Romantic poet, famously grappled with the subjects of youth and age, innocence and experience, and static and dynamic beauty in his 1819 poem, "Ode on a Grecian Urn."[1] Cosmetic dermatologists, too, regularly face these subjects as they consider the appropriate and ideal treatment of the aging face. Dynamic rhytides are approached with chemodenervation injectable therapies while static rhytides are treated with soft-tissue augmentation or volumization. With the development and approval of hyaluronic acid (HA) fillers in the United States over the past decade, patients may opt for a product that allows for a natural nonsurgical restoration of youthful facial contours. The HA fillers offer a smaller risk of the hypersensitivity reactions associated with the older bovine collagen fillers and a longer-lasting result.[2-4] As with any innovation, essential criteria in the adoption of a cosmetic filler include facility of use, longevity of results, and minimization of adverse effects. The current HA fillers more than adequately fulfill these objectives, thus accounting for their popularity. We add a succinct review of the properties of HA fillers, several current techniques and patterns of injection, and potential complications associated with HA filler use. We further point out some of the future directions for HA filler application.

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PROPERTIES

Physiologically, HA is a glycosaminoglycan present in the dermis, alongside dermatan sulfate, heparin, heparan sulfate, keratan sulfate, and chondroitin 4– and chondroitin 6–sulfates.[5] Hyaluronic acid and dermatan sulfate are the most abundant of the glycosaminoglycans. Structurally, HA is represented by a lengthy chain of repeating nonsulfated disaccharides (glucuronic acid, N-acetylglucosamine.) This is consistent across all species and tissues. While many of its functions are still not completely understood, it is known that HA binds to water and provides the dermis with volume, functioning in sodium and water homeostasis as well as protection against dermal compression.[5] Similarly, injectable HA is hygroscopic and has been said to bind up to 6 L of water per gram.[6] The injectable HAs most widely used at present are bacterially derived from *Streptococcus equi* cultures rather than from the avian combs of initial products. The bacterially derived HAs must be stabilized to prevent their prompt degradation, hence are called nonanimal stabilized HAs. There are various means of stabilization employed by the different nonanimal stabilized HAs and different stabilizing chemicals may be used, including butanediol diglycidyl ether, divinyl sulfone, and bis carbodiimide. Butanediol diglycidyl ether is most commonly employed.[7] The stabilizer varies in many of the products on the market today, as does

the proportion of stabilized and unstabilized HA; thus, each product may have a different viscosity and longevity.[8]

At present, the injection of HA fillers is said to be the second most popular nonsurgical cosmetic procedure in the United States, following only the injection of botulinum toxin.[9] As of January 2009, 9 HA injectables have been approved by the US Food and Drug Administration. These include Restylane, Perlane, Hylaform, Hylaform Plus, Captique, Juvéderm Ultra, Juvéderm Ultra Plus, Elevess (now called Hydrelle), and Prevelle Silk. Hylaform, Hylaform Plus, and Captique are no longer on the market. Each of these fillers has distinct intrinsic properties, including the size of the particulate matter, the method of cross-linking, the amount of hydration within the syringe itself, and consequently the stiffness or rheology of the filler (dependent on both the cross-linking and hydration)[10-13] (Table). As Brandt and Cazzaniga[14] recently wrote, "It is important to keep in mind that not all HA fillers are created equal." Core clinicians must maintain a familiarity with the properties of each of the approved fillers to best choose the optimal filler for the region of the face to be corrected.

CURRENT TECHNIQUES

All of the HA fillers are indicated for the correction of facial rhytides. At present, there is an emphasis on augmentation of the cheeks as a scaffold for the midface, rather than a singular focus on the nasolabial folds.[15] This is based on the anatomic studies of Rohrich et al,[16] which examined the midfacial fat compartments and determined that the loss of the deep fat in the medial cheek creates pseudoptosis of the skin and prominence of the nasolabial fold. Solish et al[17] devised a grading scale for evaluation of the malar crease, pointing out that HA fillers may correct moderate to severe malar creases in layers, with superficially placed HAs layered on the more robust HA products.

Another relatively new area for HA volumization is the lateral brow. With resorption of the lateral brow fat pad and solar elastosis, the brow and upper lid become ptotic. Surgical correction is the conventional treatment, but volumization may forestall the need for such surgery. Carruthers and Carruthers[18] explain their technique for filling the lateral brow in a 2005 review, advocating a "push-ahead" method of adding filler to the subdermal space at the level of the supraorbital ridge. They suggest that the HAs are ideal for this anatomic region because their viscosity decreases the likelihood of embolization and vascular occlusive phenomena periorbitally.[18]

Early in the adoption of HA fillers, there was concern that injection below the dermis would result in a waste of product and suboptimal correction of the flattened contour. A 2008 paper by Arlette and Trotter[19] refuted this notion. They histologically examined injected tissue that had been excised in the context of Mohs micrographic surgery. The nasolabial fold was injected to achieve adequate contour improvement. The authors suggest that in spite of the injector's expectation that the filler was implanted in the deep dermis, in fact, most of the time the filler was largely injected just below the dermis. They postulate that the injection of newer HA injectables, with more cross-linking, may prevent a more rapid metabolism at deeper locations.[19]

There is anecdotal concern that the implantation of HA fillers and subsequent laser, radiofrequency (RF) or intense pulsed light (IPL) treatment may affect or negate filler treatment. Goldman et al[20] set up conditions to test this concern. They injected the nasolabial folds and postauricular areas of 36 volunteers with HA bilaterally, subsequently performing treatment with a 1320-nm Nd:YAG laser, 1450-nm diode laser, monopolar RF, and IPL on one side. A blinded investigator then assessed each patient at various time points up to 56 days posttreatment. Histologic assessment was performed at 0, 14, and 28 days posttreatment, and additional laser treatment was performed at day 14. There was no difference in either side by blinded investigator, patient, or histologic assessment. The authors concluded that the safety and efficacy of HA implants are unaffected by direct laser, RF, and IPL treatments.[20]

COMPLICATIONS

Any potential injector must have a thorough appreciation of the potential complications that may arise. An understanding of the pitfalls of HA-filler use, however rare these may be, allows for the prompt and appropriate management of adverse events. Photographic documentation before and after the procedure may be valuable.

As with any injectable product, placement of an HA filler may cause immediate erythema and swelling, and immediate or delayed bruising. Patients may be told to stop medications and herbal supplements that may contribute to bruising, with input from a primary clinician or cardiologist if necessary. In general, erythema, swelling, and bruising resolve within a few days to a week after injection. Some authors consider these "normal and common sequelae" of injection, rather than complications, as they are so frequent and to some degree, expected.[21]

Other more serious, less frequent complications of HA injection include contour defects, migration of product, a bluish discoloration secondary to the Tyndall

Hyaluronic Acid Filler Properties

Filler (Company)	FDA Approved/ Year	Available on Market	Derivation	Average Particle Size, µm	Particles per mL (Concentration)	Cross-linker	Degree of Cross-linkage, %	Contains Anesthetic	Other Additive
Restylane (Q-Med; Medicis)	Yes/2003	Yes	Bacterial	300	100,000 (20 mg/mL)	BDDE	1	No	No
Perlane (Q-Med; Medicis)	Yes/2007	Yes	Bacterial	650	10,000 (20 mg/mL)	BDDE	1	No	No
Hylaform (Genzyme; Allergan)	Yes/2004	No	Avian	500	NA (5.4 mg/mL)	DVS	12	No	No
Hylaform Plus (Genzyme; Allergan)	Yes/2004	No	Avian	700	NA (5.4 mg/mL)	DVS	12	No	No
Captique Genzyme; Allergan)	Yes/2004	No	Bacterial	500	NA (5.4 mg/mL)	DVS	20	No	No
Juvéderm Ultra (Corneal; Allergan)	Yes/2006	Yes	Bacterial	NA	Nonparticulate; 24 mg/mL	BDDE	6	No	No
Juvéderm Ultra Plus (Corneal; Allergan)	Yes/2006	Yes	Bacterial	NA	Nonparticulate; 24 mg/mL	BDDE	8	No	No
Elevess (now Hydrelle) (Coapt Systems; Anika Therapeutics)	Yes/2006	Yes	Bacterial	200	NA (28 mg/mL)	BCDI	Unavailable	Yes	Sulfites
Prevelle Silk (Genzyme; Mentor Corp)	Yes/2008	Yes	Bacterial	350	NA (5.4 mg/mL)	DVS	12	Yes	No
Puragen Plus (Mentor Corp)	No/awaiting approval	No	Bacterial	40–250	NA (20 mg/mL)	DEO (2-stage)	Unavailable	Yes	No

Abbreviations: FDA, US Food and Drug Administration; BDDE, butanediol diglycidyl ether; NA, not available; DVS, divinyl sulfone; BCDI, bis carbodiimide; DEO, diepoxyoctane.

effect, and nodule formation (sometimes referred to as "angry red bumps"[22]). Angioedema after lip injection with HA also has been reported.[23] Like any procedure in which the skin is penetrated, infection may occur, and caution should be taken in patients receiving immunosuppressive medication. Prophylaxis is advised in patients with frequent herpes simplex virus outbreaks.

The most feared of all injectable complications are vascular occlusion with resultant necrosis and potential embolization of the filler, which under some conditions may lead to blindness. While there is no fail-safe means of avoiding these or any of the aforementioned complications, there are precautions that should be taken to minimize serious adverse effects. Slow, careful injection and an appreciation of the anatomy of the face stand chiefly among them. There are a number of important articles regarding the prevention of and approach to filler complications in the dermatologic literature that should be keenly studied.[21,24,25]

The use of hyaluronidase in the integrative approach to filler complications deserves mention. Hyaluronidase, a soluble enzyme derived from mammalian testes, has been used in nerve block anesthesia and in ophthalmic surgery to increase tissue permeability.[26] Diluted with lidocaine or saline, it may be injected in small quanta to dissolve HA when filler is placed inappropriately.[27] Hyaluronidase injections may be used in combination with nitropaste, warm compresses, and massage when an occlusive process is progressing.[28] The enzyme has been further used in the context of nodular reactions to filler that may represent biofilms, alongside incision/drainage and antibiotics.[29] While hypersensitivity reactions to hyaluronidase may occur, at times the need for dissolution of the filler may outweigh the need to proceed with prior intradermal skin testing and the physician must consider the risks and benefits of such use.

FUTURE DIRECTIONS

In a 2009 review, Tammi and Tammi[30] reflect on data to show that endogenous HA is plentiful in fetal development, and similarly, that HA deposition is induced in the postnatal wound-healing environment by epidermal growth factors. They indicate that HA induction aids in epidermal regeneration and suggest that further research is needed to examine whether exogenous HA may provoke a similar regenerative pattern.[30] Early clinical observations have suggested that this may be so. In a 2007 study of 11 healthy volunteers, HA was implanted in photodamaged forearm skin and specimens were biopsied 4 and 13 weeks later.[31] The HA injected sites were associated with increased procollagen gene expression, increased deposition of type I collagen, and stretched fibroblasts, all indicative of a synthetic response. A 2008 study took these results one step further, assessing elasticity, skin surface morphology (roughness), and skin thickness and density in 19 female participants after 3 injection sessions of HA in the lower cheeks, spaced 4 weeks apart.[32] While skin density and thickness remained fixed, both elasticity and roughness substantially improved. Even more recently, in a 2009 study of 16 women with moderate to severe brachial ptosis, 1 mL of HA was injected over a 10×6-cm space on each arm at each of 3 sessions.[33] The authors then measured elastic parameters ultrasonographically and employed corneometry to assess hydration at a 90-day follow-up visit. They found that by all measures (hydration, thickness, elasticity), as well as clinically, skin texture was substantially improved.

The findings of these and other investigations, which maintain that HA deposition not only may temporarily improve facial contours but also may stimulate endogenous volumization and improve textural parameters, have far-reaching implications. There is little doubt that the importance of HAs will continue to expand not only in the improved treatment of facial rhytides and photoaging but perhaps also in camouflaging the appearance of cellulite and managing atrophic skin diseases.

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