Chapter

Hyaluronic Acid Fillers: Where We Have Been and Where We Are Going

Alexander Daoud and Robert Weiss

Abstract

Since the approval of the United States' first hyaluronic acid (HA) filler in December 2003, HA fillers have become mainstays of soft tissue augmentation due to their favorable safety profile and minimally invasive treatment nature. The past two decades have not only brought an expansion in the popularity of HA fillers, but also in the number of available HA filler products and indications for cosmetic enhancement. Accordingly, HA filler injection has become one of the most commonly performed cosmetic procedures worldwide. The progression of HA filler products is a study in both biomedical engineering advancements, as well as evolving concepts of beauty and cosmesis. In this chapter, we review the history of these products, including their composition and indications for use. We then explore the prospect of HA fillers for the future of esthetic medicine, as they remain a vital component of nonsurgical soft tissue augmentation.

Keywords: soft tissue augmentation, biomedical engineering, cosmetic dermatology, hyaluronic acid

1. Introduction

Although typically thought of as outgrowths of modern medicine, interventions for esthetic and cosmetic purposes are well documented through multiple civilizations across history. In the non-surgical arena, soft tissue augmentation rapidly accelerated with the first reports of autologous fat transfer in the late 19th century; concomitantly, reports began to emerge from Europe on the use of injectable paraffin for rhytide reduction and soft tissue rejuvenation [1]. Shortly after the spread of paraffin injections across Europe and Asia, reports of embolic complications, as well as late-onset granulomatous reactions (later called 'paraffinomas') led to their eventual removal from the realm of esthetic practice, although non-medical/illicit injection of paraffin-containing substances still remain a sporadic issue in clinical practice today.

It was not until the 1940s that a new injectable agent found widespread use. Silicone, a dimethylsiloxane polymer, first entered clinical practice in Japan as an agent for breast augmentation. Over the following twenty years, silicone found widespread popularity across the United States, with the Dow Corning Corporation developing an injectable form of the material in the mid-1960s. As with paraffin decades prior, reports began to emerge in the 1960s–70s of delayed granulomatous

reactions to injected silicone. Termed *siliconomas*, these entities displayed a similar inflammatory pattern to paraffin, although migration of silicone due to the effects of gravity often led to granuloma formation at a site inferior or distal to the original site of injection [2]. As with paraffin, illicit silicone injection remains an issue across the world today, and clinicians should be mindful of this entity in the evaluation of granulomatous reactions following non-medical cosmetic treatments.

In 1981, the cosmetic landscape advanced with the United States Food and Drug Administration's (FDA) approval of Zyderm™, the first injectable filler approved for facial cosmetic enhancement. Derived from bovine collagen, Zyderm™ was comprised of a matrix of type I and type III collagen, which later formulations (Zyplast™) cross-linked with glutaraldehyde in order to slow the degradation of injected material [2]. Unlike the relatively inert nature of both paraffin and silicone, bovine collagen poses a significant risk of hypersensitivity reactions (3–3.5%, per population estimates) due to cross-speciation. Accordingly, skin testing prior to injection was necessary for all patients. Furthermore, although the collagen used for injection was derived from a closed and closely surveilled group of bovines, public concern regarding bovine spongiform encephalopathy ("mad cow disease") led to its fall from favor across the following decades [2].

The modern cosmetic injectables revolution found its genesis in 2003, when the FDA approved Restylane™, its first hyaluronic acid (HA) product. While other non-HA fillers were approved by the FDA for use in the following years – poly-L-lactic acid (Sculptra™), polymethylmethacrylate (Belafill™), and Radiesse™ (calcium hydroxylapatite) among the most commercially successful – HA fillers have risen as some of the most popular agents available for nonsurgical facial cosmesis.

2. Hyaluronic acid fillers: derivatives and bioengineering

Hyaluronic acid is a glycosaminoglycan, a type of acid mucopolysaccharide that demonstrates significant hydrophilicity and serves as a key portion of the extracellular matrix of all organisms. In skin, HA is a key component of "ground substance", the acellular material found in the extracellular environment around collagen bundles of the dermis. In its structural support of collagen and elastin fibers, HA's main role in skin is to lubricate these extracellular structures by attracting water, which in turn produces a volumizing effect in the skin [3].

With time, the amount of HA in the dermis begins to diminish; accordingly, a hallmark of aging skin is a loss of both volume and elasticity. To this effect, HA fillers rose as a safe and logical solution for facial soft tissue enhancement: by reinstating the HA balance of the dermis, HAs draw water into the extracellular environment and lead to significant improvements in rhytide and soft tissue [2, 4]. Furthermore, due to HA's ubiquitous nature as a 'native component' of skin, the immunogenicity of HA filler products remains extremely low.

Engineering of HA fillers is possible through two broad methods: animal-derived and bacterial-derived HAs. In the animal-derived group, HA is extracted from rooster combs and used for cosmetic injection [5]. Among the most successful in this group is Hylaform™, although animal-derived HAs have fallen from popularity due to their relatively shorter duration of effect, as well as their slightly increased immugenicity as compared to bacterial-derived HAs [1, 2]. In the bacterial-derived group, HAs are typically generated by fermentation of nonanimal stabilized hyaluronic acid (NASHA) from streptococcal species (Restylane™, Juvederm™, Captique™, Hydrelle™).

Two unique variables that determine an HA filler's physical properties are gel particle size, as well as the degree of HA crosslinking present. This is best

exemplified by the Restalyne™ and Juvederm™ line of HA fillers, where adjustments in these two variables are used to create novel products with different properties and clinical applications. While many other HA filler products are commercially available, further analysis of this line of HA filler agents is chosen due to their ubiquitous presence in cosmetic offices worldwide.

Alterations in gel particle size are a hallmark of the Restylane™ family of products: products featuring particles of lower molecular weight (350 μm for Restylane™ versus 800-900 μm for Restylane™Lyft [formerly known as Perlane]) allow for a higher density of gel particles per unit volume (100,000 particles/milliliter for Restylane™ versus 8,000 particles/milliliter for Restylane™Lyft). This is engineered through a process of sieving – by filtering particles mechanically, products are created with gel particles of a singular size [6]. Accordingly, while small gel particle-based products such as Restylane™, Restylane™-L, Restylane™ Kysse, and Restylane™ Silk have been approved for applications ranging from midface to lip and perioral augmentation, larger gel particle products such as Restylane™ Defyne, Restylane™ Refyne, and Restylane™ Lyft has been typically employed for deep rhytide correction and volumization of the cheeks and midface. Notably, Restylane™ Lyft also carries FDA approval for dorsal hand rejuvenation [1, 6, 7].

The effects of varying degrees of crosslinking are best displayed by the Juvederm™ family of products. Generally speaking, the greater the degree of crosslinking, the greater the degree of water absorption demonstrated by the filler; accordingly, more crosslinked products are typically used when significant volumizing or deep rhytide correction is desired. In contrast to Restalyne, which maintains the same concentration of hyaluronic acid throughout its product line, Juvederm™ products feature varying concentration of hyaluronic acid (24 mg/mL for Juvederm Ultra, Juvederm Ultra Plus, Juvederm Ultra XC, and Juvederm Ultra Plus XC; 20 mg/mL for Juvederm Voluma; 17.5 mg/mL for Juvederm Vollure; 15 mg/mL for Juvederm Volbella). In addition, these products also differ from each other in both their percentage of HA crosslinking, as well as the manner in which they are crosslinked [8, 9].

Juvederm Ultra, Ultra Plus, and their XC variants feature a patented crosslinking technology termed Hylacross. With Hylacross, HAs of the same molecular weight are crosslinked together, creating a relatively uniform product of set viscosity and thickness. This is in contrast to Juvederm Voluma, Vollure, and Volbella, which use another patented technology called Vycross crosslinking. Vycross-generated fillers feature HAs of varying molecular weight, resulting in products that are reported to have a greater number of applications across the face, as well as a longer duration of action due to non-uniform degradation [8, 10].

Together, it is gel particle size and density, as well as degree/type of HA crosslinking, that influence the *G'*, or elastic modulus, of HA fillers. G' is a measure of a filler's response to shear or dynamic forces: the higher the G' of a filler, the greater its resistance to deformation or movement when under the influences of external force (such as dynamic facial movement). Accordingly, fillers with higher G' are often used for their volumizing and lifting effects, and deeper injections are needed [9, 11].

Emblematic of the role of G' in filler applications, Belotero Balance (Merz Esthetics) is a HA filler product that relies on a greater density of non-crosslinked HA in order to produce its intended effect. Generally speaking, the strength and volumizing effect of fillers is directly related to its degree of HA crosslinking – that is, free HAs are non-contributory to the strength, volumizing, or lifting potential of a filler product. Through a novel, patented formulation called Cohesive Polydensified Matrix – a process that generates a varying degree of crosslinked

HA in suspension with free HAs – a product is produced that features a significantly lower G' than other HA products (G' = 30 for Belotero Balance; G' = 545 for Restylane™ Lyft). Accordingly, Belotero ™ Balance is able to be used in both the intradermal and superficial subcuticular planes, with lower risk of the Tyndall effect (a gray-blue discoloration secondary to light scattering from superficially placed filler products) as compared to other HA fillers [9, 11, 12].

Depending on the product used, as well as the location being treated, HA fillers typically augment treated soft tissues for a period of 6–18 months. As compared to bovine collagen, hypersensitivity reactions are exceedingly rare, estimated at 1 in every 5000 injections. A notable benefit of these products, as compared to non-HA fillers, is their reversibility: if dissolution of filler is needed, injectable hyaluronidase may be used.

3. Hyaluronic acid fillers: directions for the future

Given their widespread success and popularity, HA fillers are likely to remain a mainstay in the cosmetic proceduralist's toolbox. Innovations in the field – ranging from methods of biochemical engineering to novel techniques for injection and treatment – all lend great promise to the future of HA fillers in esthetic practice.

In the realm of product development, one such advancement is demonstrated by Teosyal ™, an HA filler approved by the FDA in 2017. Through a novel patented synthesis method, a product with a lower bacterial protein and endotoxin load (as compared to other HA fillers) is generated, with a reported lower risk of potential hypersensitivity reactions as a result [9]. Another product generated through a unique method of synthesis is the Neauvia ™ family of HA fillers. Marketed as a 'fully organic' product, Neauvia ™ HAs are not synthesized from the streptococcal species typical of other HA fillers, but instead by *Bacillus subtilis*, a bacterium widely used in probiotic supplements. These HAs are then crosslinked with polyethylene glycol, creating a biocompatible hydrogel [13]. Lastly, Juvederm ™ has recently introduced Volux, a thicker HA with a concentration of 25 mg/mL, for lower face (jawline and chin) augmentation.

Continuing improvements in injection technique also offer a promising future of HA filler use. Blunt-tipped cannulas are rising in popularity as an alternative to hypodermic needles, as their use is associated with a statistically significant decrease in bruising, as well as lower pain associated with injection [14]. Additionally, cadaveric studies comparing blunt-tipped cannulas to sharp needles demonstrated a higher risk of intra-arterial injection with sharp needles, as well as a greater degree of filler extrusion across multiple anatomic planes (as opposed to one targeted level of injection) with needles as compared to blunt-tipped cannulas [15]. Accordingly, the use of cannulas has greatly advanced the technique, safety profile, and resultant cosmetic effect of HA fillers to areas such as the tear troughs and jawline, where anatomic plane precision is critical.

Exactness in volumetric dosing is highly dependent on injector experience, as elements such as HA filler viscosity, needle gauge, and plane/site of injection all influence the force needed to inject a bolus of filler agent. To elevate this aspect of treatment beyond volume marking on syringes and "injector feel" while introducing a bolus, Restylane ™ has recently introduced Skinboosters, a microdroplet HA treatment that uses a SmartClick® syringe to provide metered doses with each depression of the syringe plunger [16]. This technology has especially shown great promise when injecting into more superficial planes, as improper or non-uniform technique may otherwise result in nodule or 'lump' formation, as well as the Tyndall effect.

4. Conclusions

Hyaluronic acid fillers are essential component of the cosmetic proceduralist's armamentarium. Their ubiquitous presence in clinics across the world, as well as their widespread acceptance by the general public, has made awareness of their use important for all clinicians. An understanding of their unique properties and physical features provides esthetic practitioners with a better comprehension of their treatment indications, potential complications, and treatment pitfalls, as well as an appreciation of developments on the horizon for future HA fillers.

Author details

Alexander Daoud* and Robert Weiss
Maryland Dermatology, Laser, Skin, and Vein Institute, Baltimore, MD, USA

*Address all correspondence to: adaoud@mdlsv.com

References

[1] Kim JE, Sykes JM. Hyaluronic acid fillers: history and overview. Facial Plast Surg. 2011 Dec;27(6):523-528.

[2] Kontis TC, Rivkin A. The history of injectable facial fillers. Facial Plast Surg. 2009;25(2):67-72.

[3] Zerbinati N, Lotti T, Monticelli D, et al. *In Vitro* Evaluation of the Sensitivity of a Hyaluronic Acid PEG Cross-Linked to Bovine Testes Hyaluronidase. Open Access Maced J Med Sci. 2018;6(1):20-24.

[4] Matarasso SL, Carruthers JD, Jewell ML; Restylane Consensus Group. Consensus recommendations for soft-tissue augmentation with nonanimal stabilized hyaluronic acid (Restylane). Plast Reconstr Surg. 2006 Mar;117(3 Suppl):3S-34S; discussion 35S-43S.

[5] Kang DY, Kim WS, Heo IS, Park YH, Lee S. Extraction of hyaluronic acid (HA) from rooster comb and characterization using flow field-flow fractionation (FlFFF) coupled with multiangle light scattering (MALS). J Sep Sci. 2010;33(22):3530-3536.

[6] Khosravani N, Weber L, Patel R, Patel A. The 5-Step Filler Hand Rejuvenation: Filling with Hyaluronic Acid. Plast Reconstr Surg Glob Open. 2019;7(1):e2073.

[7] Dover JS, Rubin MG, Bhatia AC. Review of the efficacy, durability, and safety data of two nonanimal stabilized hyaluronic acid fillers from a prospective, randomized, comparative, multicenter study. Dermatol Surg. 2009 Feb;35 Suppl 1:322-330; discussion 330-1.

[8] Bogdan Allemann I, Baumann L. Hyaluronic acid gel (Juvéderm) preparations in the treatment of facial wrinkles and folds. Clin Interv Aging. 2008;3(4):629-634.

[9] Rohrich RJ, Bartlett EL, Dayan E. Practical Approach and Safety of Hyaluronic Acid Fillers. Plast Reconstr Surg Glob Open. 2019;7(6):e2172.

[10] Micheels P, Besse S, Sarazin D. Two Crosslinking Technologies for Superficial Reticular Dermis Injection: A Comparative Ultrasound and Histologic Study. J Clin Aesthet Dermatol. 2017;10(1):29-36.

[11] La Gatta A, Salzillo R, Catalano C, et al. Hyaluronan-based hydrogels as dermal fillers: The biophysical properties that translate into a "volumetric" effect. *PLoS One*. 2019;14(6):e0218287. Published 2019 Jun 11.

[12] Sundaram H, Fagien S. Cohesive Polydensified Matrix Hyaluronic Acid for Fine Lines. Plast Reconstr Surg. 2015 Nov;136(5 Suppl):149S-163S.

[13] Zerbinati N, Mocchi R, Galadari H, et al. *In Vitro* Evaluation of the Biological Availability of Hyaluronic Acid Polyethylene Glycols-Cross-Linked Hydrogels to Bovine Testes Hyaluronidase. *Biomed Res Int*. 2019;2019:3196723. Published 2019 Jun 12.

[14] Fulton J, Caperton C, Weinkle S, Dewandre L. Filler injections with the blunt-tip microcannula. J Drugs Dermatol. 2012;11(9):1098-1103.

[15] van Loghem JAJ, Humzah D, Kerscher M. Cannula Versus Sharp Needle for Placement of Soft Tissue Fillers: An Observational Cadaver Study. Aesthet Surg J. 2017 Dec 13;38(1):73-88.

[16] Lee BM, Han DG, Choi WS. Rejuvenating Effects of Facial Hydrofilling using Restylane Vital. Arch Plast Surg. 2015;42(3):282-287.