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Update on Hyaluronic Acid Fillers

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Abstract Hyaluronic acids (HAs) have become the injectable filling agents of choice due to both their biocompatibility and ability to be enzymatically dissolved with hyaluronidase. Recent trends in facial analysis have resulted in injectors assessing the face in three dimensions and combining or layering different injectable products during the same treatment session. Quality of life measures confirm that patients are satisfied with the volume enhancements and facial rejuvenation they receive after injections. Increased understanding of the biophysics of HAs allows not only improved understanding of how the products act in vivo, but also allows for the manufacture of products with varying physical characteristics. Although the safety and efficacy of these products have previously been established in the scientific literature, recent studies describe both acute and chronic complications seen with these agents. In the future, HAs may be combined with tissue-engineered fibroblasts, which could improve the safety and longevity of these products.

Keywords Hyaluronic acid · Dermal filler · Filler complications · Restylane · Perlane · Juvederm Ultra · Juvederm Ultra Plus · Juvederm Voluma · Belotero Balance · Stem cells

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Introduction

The approval of the hyaluronic acid (HA) Restylane (Galderma Laboratories, Ft. Worth, TX) in 2003 by the US Food and Drug Administration (FDA) was a turning point in modern facial rejuvenation. A recent survey by the American Society of Aesthetic Plastic Surgeons (ASAPS) [1] noted the injection of HA has become the second most commonly performed non-invasive esthetic treatment in the US, second only to injectable neurotoxins. Historically, bovine collagen was the mainstay for filling lines and wrinkles but was fraught with the issues of non-biocompatibility, allergic reactions, and short-term clinical results. Hyaluronic acid, a normal skin polysaccharide, was possibly the ideal wrinkle filler because it was present in normal tissue, biocompatible, biodegradable, and provided relatively long-lasting results. Head-to-head comparisons against collagen were so overwhelmingly positive that Restylane became the gold standard against which all future dermal fillers were compared [2].

Although initially FDA approved for the nasolabial folds, clinicians found that HA fillers could be used for volume enhancement in virtually every region of the face. Occurring simultaneously was the improved understanding of three-dimensional facial aging: lipoatrophy and volume loss initially, followed by loss of bony support, and reduction of skin elasticity [3••]. The development of filling agents possessing different indications and physical properties combined with the improved undertanding of facial aging has served to enhance the current treatments for facial rejuvenation.

As we push these products to their limits, acute and long-term complications are being realized. Studies are being performed to better understand the biochemical properties of fillers and the inflammatory reactions they can

stimulate. New and improved HA products are being developed, and tissue engineering may be the future of the injectable revolution. The following will discuss these aspects of HA fillers which have been published in the literature over the past year.

Biophysics of Hyaluronic Acid Fillers

The ideal injectable filler should be non-inflammatory, biocompatible, non-carcinogenic, non-allergenic, and non-migratory. HA comes close to meeting these criteria and is considered by many injectors to be the product of choice for soft tissue augmentation. HA is a naturally occurring hydrophilic polysaccharide which comprises a large portion of the extracellular matrix in animals. Uncross-linked HA injected into the body will rapidly degrade in 1–2 days; therefore, cross-linking is essential to prevent early degradation. The most common cross-linking agent is 1,4-butanediol diglycidal ether (1,4 BDDE) which is nontoxic to humans [4].

The structure and visco-elastic properties of HA fillers vary by manufacturer which results in products possessing varying characteristics and clinical properties (see Table 1). HA fillers can be either monophasic or biphasic, depending on their amount of cross-linking. Park et al. [5] compared the monophasic HA, Juvederm (Allergan Inc., Irvine, CA), with the biphasic HA, Perlane (Galderma Laboratories, Ft. Worth, TX), and found that biphasic fillers seem to better resist degradation by hyaluronidase (HYAL), and monophasic fillers seem to provide better volume augmentation. Tran et al. [6] studied the bio-integration of HA fillers based on their cross-linking technologies by comparing products with three different manufacturing technologies [Juvederm, Restylane and Belotero (Merz Aesthetics, Inc., San Mateo, CA)] and concluded all were safe, well tolerated, and resulted in minimal inflammatory response. In addition, they noted that the cohesive, monophasic, polydensified matrix product (Belotero) showed the most homogeneous tissue integration. In a comparison of nasolabial fold treatment using monophasic (Belotero) versus biphasic (Perlane), Buntrock et al. [7] showed similar clinical results, but favoring the monophasic product in terms of patient comfort and satisfaction. In a randomized, double-blind, side-by-side comparison of Perlane versus Belotero in treating the nasolabial folds, both fillers showed improvements up to 48 weeks and after 48 weeks, the side with Belotero showed continued clinical improvements [8].

There has also been some question as to whether or not cross-linking of HA influences changes in the proliferation or metabolic activity of fibroblasts. It is possible that the proliferation of fibroblasts is stimulated by the degradation products of uncross-linked HA. In addition, the increased collagen synthesis could be achieved either by mechanical stretching of the fibroblasts or possibly from cytokine cascade [9].

Complications and Their Management

As indications are broadened for the use of HAs and as untrained or poorly trained injectors perform these procedures, the number of complications has risen. Complications of HA fillers are typically minor and self-limiting and include bruising, swelling, ecchymosis, and lumpiness. Less common complications are now being described in the literature and include visual loss, necrosis, arterial embolization, granuloma formation, migration, and allergic reactions [10, 11•, 12–15]. Vascular embolization causing visual injury or loss has been described primarily after injection of HA to the glabella [16–18], nasal dorsum [19], and forehead [20, 21]. These complications can be life threatening, as Kim et al. [22], reported of a case of severe visual loss and cerebral infarction in a 23-year-old man who underwent cosmetic nasal injection with HA.

One of the advantages of HA use is the availability of the HYAL enzyme, which can rapidly degrade the product, either in the case of inappropriate placement or vascular compromise. The treatment paradigm for acute vascular injury currently includes immediate discontinuation of injections, massage, warm compresses, HYAL injection, aspirin taken orally, and topical nitropaste [23]. Vascular injury and impending necrosis are disastrous complications. Recent literature suggests considering the use of hyperbaric oxygen treatments for impending tissue necrosis [24]. Bailey et al. [25••] discussed the use of HYAL in the cosmetic arena and concluded that HYAL had a high safety profile and should be used not only in cases of vascular injury, but also to improve product lumpiness or inappropriate placement, granulomatous reactions, and impending necrosis. Hilton [26] described the additional benefit of HYAL in the treatment of lower lid edema seen after the injection of HA to the lower lid and tear trough region. There have been no studies to confirm whether HYAL is able to cross the arterial wall, or if it should be injected directly into the occluded vessel. DeLorenzi [27] addressed this question by showing that HYAL traversed the arterial vessel walls in the cadaveric model, suggesting that intra-arterial injection may not be necessary in emergent situations.

The development of biofilms (clumps of bacteria in a polymeric gel) as a complication of filler injections has had increasing interest in the esthetic injector community. The ability for bacteria to survive and grow in many injectable products has been shown, highlighting the need for thorough antisepsis prior to injection. The route of entry of such infections is most likely through the skin by

Table 1 Comparison of physical characteristics for hyaluronic acid dermal fillers

Product (year FDA approved)	Cohesiveness[a]	Mono[b] or biphasic[c]	Manufacturing process	Particle size	Stabilizer	G′[d]
Restylane (2003) Restylane-L (2010)	Non-cohesive	Biphasic	Non-animal stabilized hyaluronic acid (NASHA)	250 μm	1,4-BDDE[e]	Medium
Perlane-L (2010)	Non-cohesive	Biphasic	NASHA	550 μm	1,4-BDDE	Medium
Juvederm Ultra (2006) Juvederm Ultra XC (2010)	Cohesive 9 %cross-linked	Monophasic	Hylacross	Blended sizes 24 mg/ml 100 % HMW[f]	1,4-BDDE	Low
Juvederm Ultra Plus (2006) Juvederm Ultra Plus XC (2010)	Cohesive 11 % cross-linked	Monophasic	Hylacross	Blended sizes 24 mg/ml 100 % HMW	1,4-BDDE	Low
Juvederm Voluma XC (2013)	Cohesive	Monophasic	Vycross	Blended sizes 20 mg/ml 90 % LMW[7] and 10 %HMW	1,4-BDDE	Low (higher than Ultra and Ultra Plus)
Belotero Balance (2011)	Cohesive	Monophasic	Cohesive polydensified[h] matrix (CPM)		1,4-BDDE	Lowest

[a] Cohesiveness refers to the ability of the product to hold its shape under stress

[b] Monophasic is a one-step production which results in a product with both high and low molecular weight particles

[c] Biphasic production is a two-step process which separates particles by size

[d] G′ (G prime) determines gel stiffness and the ability to resist deformation. Relative comparisons are made rather than numeric comparisons because testing methods vary

[e] 1,4-Butanediol diglycidal ether

[f] High molecular weight hyaluronic acid

[g] Low molecular weight hyaluronic acid

[h] Polydensified adds in more HA and additional cross-linking, resulting in double cross-linking of monophasic strands

penetration of a contaminated needle. Possibly the risk of biofilm infection increases with the increased longevity of the product [28]. Treatment of such complications requires the use of appropriate antibiotics; however, steroid injections are discouraged because the absence of inflammatory cells allows the bacteria to grow freely.

Nodule development is a complication of HA filler injection that may occur in the acute or long-term post-injection period. The early formation of nodules is generally non-inflammatory and due to the improper placement of product, whereas inflammatory nodules may occur months to years after treatment. Nodule formation is more often associated with more permanent fillers such as silicone. Despite the in vivo longevity of HA fillers of 1 year or less, inflammatory nodules may be seen even years after placement. Although HA has a low immunogenicity, delayed-type hypersensitivity can present over time as sterile abscesses, foreign body granulomas, or fibromas [29]. Histologic evaluation of HA-induced foreign body granulomas shows basophilic lakes lined by epithelioid cells [30]. Although the majority of nodules improve without treatment, possible treatment options include HYAL injection, steroids (oral, topical, injected), and antibiotics. If necessary, nodule excision may be required.

Migration of HAs superficially or inadvertent superficial placement may result in the Tyndall effect: a bluish hue seen through the skin. Delayed migration has been seen up to 5 years after initial placement [31]. It is believed that the particles from biphasic filling agents refract blue light causing the discoloration seen. Because they do not have symmetrically sized particles, it is believed that the monophasic HAs are less likely to cause this phenomenon.

New technologies are being used to assess the subcutaneous location of fillers over time, including ultrasound [32, 33], optical coherence tomography [34], and MRI [35]. Cadaveric studies also have shown the location of HA following injection to the tear trough and brow. Griepentrog et al. [36, 37] analyzed filler location after fillers had been injected into cadaver specimens. They found that HA was deposited more superficially than where the injector had intended when injecting the tear trough, however, the HA was placed in the intended plane when the brow was injected. They surmised that the dense retro-orbicularis fat septi in the brow prevented the HA from migrating superficially. In a study of tear trough injections, ultrasound evaluation revealed that although filler was placed preperiosteally, the product was actually intramuscular

[33]. This may account for the migration and occasional Tyndall effect seen with filler placed in this region.

Expression (Enhancement Medical, LLC) is a new HA developed for use as an intranasal splint following septoplasty. The FDA was alerted that some practitioners used this product "off label" as a dermal filler and complications had been reported which included erythema, itching, and the presence of firm nodules. Although these complications are not unlike those of currently FDA-approved HA fillers, on August 5, 2014, the FDA mandated that Expression was unsafe to use as a dermal filler and such off-label treatments should be discontinued until product safety has been adequately studied [38].

New Hyaluronic Acid Products

Probably the most significant development in the world of injectables is the change in focus from looking at the face in two dimensions to thinking in three dimensions. The improved understanding of facial aging and volume loss from fat pad lipoatrophy contributed to the development of a new class of HA fillers (Juvederm Voluma) with a new indication of midface volume enhancement. Juvederm Voluma is manufactured by proprietary Vycross technology which serves to cross-link both low and high molecular weight HAs into a strongly cohesive material with a high lifting capacity. This HA was specifically developed to provide "lift "to the midface and cheeks. In 2013, Juvederm Voluma became the first HA to receive FDA clearance for facial volumization. Studies assessing efficacy, safety, and patient satisfaction are promising for this new class of filler [39–41]. The pivotal study was a multi-center, single-blind controlled, randomized study of 235 patients with midface volume deficit treated with Juvederm Voluma [42•]. Response was defined as a 1 point or more improvement in the Mid-Face Volume Deficit Scale as rated by two blinded investigators at 6 months. At the 6-month evaluation, 85.6 % of patients improved by at least one point on the scale, and by 2 years, nearly half of the subjects maintained their correction.

As the midface became more popular as an injection site, new sub-areas of treatment have been described: the zygomaticomalar, anteromedial, and submalar. Glaser et al. [43] performed a multi-center trial treating the sub-regions with Juvederm Voluma and determined that for patients who received a median of 1.9 ml of product in the zygomaticomalar region, they retained a median duration of correction for 19 months. For the anteromedial cheek, a median of 1.7 ml volume produced results with median duration of 24 months and similarly for the submalar region, 2.0 ml produced results for 15 months. Three-dimensional facial esthetics is also realized in the Asian population, which typically manifests a somewhat flattened midface. These patients also had improvement using volumizing HA fillers in the midface [44].

Belotero Balance, FDA approved in 2011, has undergone rigorous clinical studies in recent years. This class of HA is monophasic, highly cross-linked, and created by cohesive polydensified matrix (CPM) technology. Safety profiles were compared between Juvederm, Restylane, and Belotero, and all were found to have similar efficacy and safety profiles. Results of a 5-year retrospective safety review in 317 patients showed no severe events, and no development of persistent nodules or granulomas [45]. Injection technique of Belotero was studied by Micheels et al. [46] who injected the epidermis and superficial reticular dermis with Belotero. Histologic analysis showed full integration of the product in the reticular dermis. The authors suggested an injection technique they described as 'blanching" to aid in placement of product into the superficial dermis. The safety of Belotero was also established for patients with darker skin types [47].

New Uses and Techniques

Subtle differences in filling agents allow the clinician to tailor their treatment to the individual patient's needs. Currently, injectors are often using different filing agents and adding the use of neurotoxins during the same injection session. As injectors become more comfortable with fillers and neurotoxins, patients are receiving a combination of these products to produce what some have called the "liquid facelift."

Although many injectors have known that a combination of neurotoxins and HA in the glabella will improve refractory glabellar lines, Dubina and colleagues [48] proved this was true in a split-face randomized controlled trial and noted increased persistence of results when the combination of products was used. Combination therapy is also described to treat peri-oral rhytids by injection of small amounts of neurotoxin as well as volumization with HA fillers [49]. Panfacial rejuvenation can be produced by combining the effects of multiple filling agents with or without neurotoxins [50, 51].

New indications for HA use have been documented in the recent literature, as well. Volumization of the earlobes has been described as a novel use for HA fillers [49]. Restoration of temple volume loss was also performed with HA filling agents [52]. Non-surgical rhinoplasty is increasingly described [49, 53, 54], as well as the devastating complications which can ensue.

The increased understanding of three-dimensional volume loss has aided in the treatment of lipoatrophy seen in chronic diseases. The combination of HA and poly-L-lactic acid to treat lupus-induced facial atrophy was reported by

Estham et al. [55]. Although this is an inflammatory disease of the subcutaneous tissue, fillers were successfully used for facial volume restoration without sequelae.

Lip enhancement with HAs is a commonly performed. Although most fillers have FDA clearance only for the nasolabial folds; Restylane was FDA approved for lip augmentation in 2011. When injected in the lips, Juvederm Ultra was also found to be safe and effective, with results lasting up to 24 weeks for over 50 % of subjects [56].

A novel approach known as mesotherapy has also been discussed in recent literature. Improvement of skin texture and quality may be improved using HA as part of a mesotherapy injection regimen. Savoia et al. [57] described using two formulations of mesotherapy containing HAs. The first formulation contained HA, vitamins, amino acids, minerals, coenzymes, and antioxidants. The second formulation contained only HA and idebenone (synthetic analog of CoQ-10). Fifty patients were divided into two groups and four sessions of treatment by multiple intradermal injections were performed on the face, neck, and décolleté. Before and after photographs were evaluated at 0, 1, and 2 months using the Wrinkle Severity Scale and the Global Aesthetic Scale. Although there was no control group in this study, the improvements noted in the GAIS scale results by blinded observers showed a statistically significant improvement in skin quality after four treatments. Histologic assessment performed on randomly selected subjects at baseline and at 6 weeks confirmed an increase in Type I collagen.

Outcomes Analysis

Quality of life (QOL) predictors have become important in assessing the perceived results after injection of fillers and neurotoxins. Injectors believe that such injections improve their patients' self-esteem and overall quality of life. In a study of 40 female adult patients who underwent filling with HA and neurotoxin injections, these minimally invasive procedures improved patient QOL and self-esteem for the first 3 months post-injection [58]. These parameters remained higher than the pre-injection levels even 6 months post-injection. Injection of fillers and neurotoxins was shown to be both effective and safe in post-chemotherapy patients, as well [59].

Severe volume depletion of the midface can contribute to patient overall satisfaction with their appearance and self-perception of age. Outcomes analysis was performed on 235 patients who were injected with Juvederm Voluma and their overall satisfaction with their appearance was measured over time [60]. Pre-injection, the patients complained they looked tired, sad, and unattractive and older than they wanted to appear. Satisfaction with their appearance was improved in 90 % of patients at 6 months, and 76 % at 2 years. Patients reported they looked 5 years younger at 6 months and 3 years younger at 2 years.

Tissue Engineering: The Future of Fillers?

HAs have been combined with acrylic hydrogels in order to increase the longevity of clinical results. Both ethylmethacrylate and polyhydroxyethylmethacrylate have been combined with HA and are used as filling agents, however, the incidence of foreign body granulomas increased, in both the acute and chronic settings [29]. Treatment of these nodules included antibiotics, corticosteroids, and 5-fluorouracil.

While still in the experimental phase, the future of fillers may include the addition of stem cells to filler material. Using a rat model, Pietkun et al. [61] injected HA both with and without adipose-derived stem cells and fish collagen also with and without stem cells into the animal's glabella, dorsum, and chest. The filling effect noted was longest for the two groups with stem cells added. Most importantly, at 3 months there were no complications, adverse effects, or distant migration noted to brain, kidneys, and lungs.

Conclusion

Hyaluronic acids are now widely accepted as safe and effective dermal filling agents. QOL studies confirm patient satisfaction with the effects they receive from dermal filler injections. However, no treatment should be considered to be without risk. Increasing reports of severe acute and chronic complications are reminders that injectors should have clear understanding of the products' uses and emergency treatments to prevent severe sequelae in cases of vascular injury. As the science of tissue engineering progresses, the future composition of filling agents may result in improved outcomes and safety.

Compliance with Ethics Guidelines

Conflict of Interest Theda Kontis reports personal fees from Allergan, Inc, and personal fees from Galderma Laboratories, outside the submitted work.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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