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REVIEW

Long-term efficacy, safety and durability of Juvéderm® XC

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Abstract: Over the last decade, there has been increasing interest in minimally invasive cosmetic treatments, especially for facial rejuvenation. Next to botulinum toxin injection, the injection of soft tissue fillers is the second most frequent minimally invasive procedure performed in the USA. Hyaluronic acid (HA) is the most commonly used dermal filler. One of patients' main concerns about filler injections pertains to pain and discomfort. Topical anesthetics, nerve blocks, and/or the incorporation of lidocaine to the filler have been applied in order to reduce distress and pain. Despite nerve blocks being an effective form of anesthesia, they may distort the area to be treated, as well as lengthen and complicate the procedure. Studies have shown that the incorporation of lidocaine to HA fillers significantly reduces pain and discomfort. Yet, one of the dilemmas about the addition of lidocaine solution to HA fillers is the possible alteration of the physical characteristics of the product by negatively impacting the efficacy and/or duration of the filler. The concern is that the addition of lidocaine could dilute the product, creating less correction per mL, changing the product's viscosity and consequently the "lifting" ability. Also, this dilution could reduce the product's duration. There may be a difference between a physician adding an aqueous solution into a lidocaine-free version of HA and the pre-incorporated lidocaine version of HA. An aqueous solution might dilute the product, while the pre-incorporated powder lidocaine appears to avoid this problem. Juvéderm® XC is manufactured with powder lidocaine 0.3%; it is associated with significantly less injection pain than Juvéderm® and other lidocaine-free versions of HA. Studies have shown that lidocaine enhances treatment comfort and optimizes the injection experience while maintaining a similar safety and effectiveness profile. Regarding the longevity, further study is necessary to determine if there is any difference in durability.

Keywords: dermal filler, hyaluronic acid, Juvéderm XC, lidocaine, Juvéderm, dermatologic procedures

Introduction

Over the last decade, there has been increasing interest in minimally invasive cosmetic procedures, especially for facial rejuvenation. Office-based, minimally invasive treatments can promote a youthful appearance with minimal downtime and low risk of complications. Next to botulinum toxin injections, the injection of soft tissue fillers is the second most frequent minimally invasive procedure performed in the USA. Dermal fillers afford aesthetic physicians the ability to treat rhytides, scars, and volume deficiency, as well as sculpt the face and augment specific anatomical sites such as the lips. The overall number of procedures in the USA using soft tissue fillers increased 190% in the last decade.[1] In 2011, 69% of all the dermal fillers injected in

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the USA were hyaluronic acid (HA), which makes HA the most commonly used soft tissue filler.[1,2]

Background

Hyaluronic acid has been cleared for use as a soft tissue filler by the US Food and Drug Administration (FDA) for nearly a decade. The first HA dermal filler to be approved by the FDA was Restylane® (Medicis Aesthetics, Scottsdale, AZ, USA), in the year 2003 (see Table 1), for correction of moderate to severe facial wrinkles and folds. HA is a non-sulfated glycosaminoglycan, a polysaccharide consisting of repeating D-glucuronic acid and D-*N*-acetylglucosamine disaccharide units. It is an essential component of the extracellular matrix of all adult animal tissues and is the most abundant glycosaminoglycan found in the human dermis. Approximately 50% of the total HA concentration in the body is located in the dermis.[3] It is an extremely hygroscopic molecule, binding up to one-thousand times its weight in water. This property allows it to contribute to the hydration and volume of tissues, as well as providing structural support. The chemical structure of naturally occurring HA's is always the same regardless of the species and type of tissue of origin. Only the molecular weight varies among different species, and is always non cross-linked. The non cross-linked hyaluronic acid, also called free form or non-modified HA, is a viscous liquid that is completely metabolized a few days after injection into the skin. It is broken down by free radicals and enzymes such as hyaluronidase that are naturally present in the skin.[4] The short life of free HA makes it undesirable and unfeasible for facial contouring and rejuvenation purposes.

The current FDA approved HA injectable fillers that are available to the practitioners are cross-linked to provide longevity. All of them are bacterially derived via fermentation of equine *Streptococcus*. Most products use 1,4 butanediol diglycidyl ether (BDDE) as the cross-linking agent (see Table 1) for the production of intermolecular bonds that create a longer, more stable molecule, and transform the viscous liquid into a gel. All HA soft tissue fillers are considered gels because they are particles (a solid phase) suspended in a fluid phase.[5] Each HA dermal filler uses different cross-linking technologies.

Depending on the cross-linking technology applied, HA soft tissue fillers can be classified into two types of gels: biphasic and monophasic, as shown in Table 1.[6] Whereas biphasic gels contain an average size of particles, monophasic gels consist of a broad distribution of gel particle sizes. Among the most commonly used FDA approved HA fillers, Restylane® and Perlane® (Medicis Aesthetics) are examples of biphasic products. Their cross-linking step produces a large, connected gel mass that takes the shape of the container in which it is formed.[7] That large gel piece must be 'sized' to allow for injection into the skin. Biphasic gels are 'sized' by passing the gel mass through a series of sieves, producing gel particles of a well-defined, average size.[4] Monophasic gels do not have to be 'sized' because they are made by a different cross-linking process. Monophasic fillers can be classified as polydensified or monodensified.[6,8] Belotero® (Merz Aesthetics, Inc, San Mateo, CA, USA) is at present the only monophasic polydensified gel approved by the FDA. It is produced by two steps of cross-linking. The first step involves the cross-linking of a determined amount of HA. In the second step, a new amount of HA is inserted and additional cross-linking is performed. Conversely, monophasic monodensified gels, such as the Juvéderm® dermal filler family (Allergan, Inc, Irvine, CA, USA), are produced by mixing the HAs and cross-linking them in just one step.[6]

It remains debatable the effect that cross-linking technology has on fillers' performance, and the influence it has on the efficacy and durability of the filler product. Flynn et al[6]

Table 1 Characteristics of most commonly used FDA-approved hyaluronic acid dermal fillers

	Restylane®*	Perlane®*	Juvéderm® Ultra*	Juvéderm® Ultra Plus*	Belotero®
Manufacturer	Medicis	Medicis	Allergan	Allergan	Merz
FDA approval	2003	2007	2006	2006	2012
HA concentration	20 mg/mL	20 mg/mL	24 mg/mL	24 mg/mL	22.5 mg/mL
Form	Particle 125 μm 100,000/mL	Particle 325 μm 10,000/mL	Homogeneous	Homogeneous	Homogeneous
Cross-linker	BDE	BDE	BDE (9%)	BDE (11%)	BDE
Type of gel	Biphasic	Biphasic	Monophasic monodensified	Monophasic monodensified	Monophasic polydensified
Gel hardness	513 Pa**	541 Pa**	28 Pa**	75 Pa**	–

Notes: *The manufacturers of Restylane-L®, Perlane-L®, Juvéderm® Plus XC, and Juvéderm® Ultra Plus XC claim that these products have the same characteristics as their respective lidocaine free versions; **Sundaram H, et al.[5] – this information is not available.
Abbreviations: BDE, 1,4-butanediol-diglycidyl-ether; FDA, Food and Drug Administration.

injected HA soft tissue fillers with differing production technologies into the human dermis and studied their diffusion through histological assessments of dermal punch biopsy samples. They considered that the diffusion of the HAs into the skin differed according to the HA's cross-linking method. Biphasic gels showed deposition in big pools, often deep in the reticular dermis. Monophasic monodensified gels demonstrated large pools of hyaluronans throughout all the thickness of the reticular dermis. Monophasic polydensified gels penetrate into the reticular dermis in a diffuse, evenly distributed manner.[6]

One might believe that a more diffuse distribution of the product into the dermis, achieved by the monophasic gels, may lead to a more even therapeutic effect. Prager et al, in a split-face study, showed that in fact 4 weeks after the injection of HA soft tissue filler into nasolabial folds, a monophasic gel presented a more desirably even clinical result than a biphasic gel.[9] However, the same study concluded upon conducting follow-ups at 6, 9, and 12 months after the treatment that the injection of both types of HA soft tissue fillers, biphasic and monophasic gels presented equivalent clinical results.[9]

As previously stated, the technology of cross-linking differs among the various HA preparations available in the market. Moreover, there are also differences in the degree of cross-linking, HA concentration, amount of free HA present, and HA particle size (see Table 1). All these factors are important in determining gel hardness and longevity, which in turn can guide the physician's decision regarding the type of filler to be selected for a particular patient or indication.[10]

G prime is the technical 'hardness' of the gel, or the amount of force required to displace two plates with gel in between the plates.[4] Products with high G prime are better able to resist outside forces and provide better structure than fillers with low G prime. The higher G prime products are better at lifting and are frequently used for producing a lifting effect in the cheeks and oral commissures. The lower G prime fillers are softer and diffuse into the skin more evenly. They are also frequently injected in the skin to correct more superficial wrinkles or for diffuse filling.[10] The G prime of the product does not affect the longevity of the product. Longevity is based on stabilization of the HA itself, which may be determined by the type and amount of cross-linking. Although uncross-linked HA injected into the skin lasts only a few hours, its inclusion in the syringe is important to assist in flow of the product from the syringe.[5,10]

Products with bigger particle size, higher cross-linked, higher G prime, and more concentration (more particles/mL) are indelibly more robust and dense. The more dense the filler material, the more profoundly it will be deposited in the skin. Therefore, dense fillers are beneficial for filling deeper wrinkles and softer gels are better suited for more superficial use. The skin thickness also can influence which filler the physician chooses for a particular patient.[11] The thinner the skin, the higher the probability is that the product may become visible, thus a softer product is preferable.

Juvéderm® dermal filler family

Juvéderm® dermal fillers are a monophasic monodensified gel, manufactured by a homogenization process, known as Hylacross™ technology, which produces a cohesive gel with a smooth consistency.[12] They have been on the market in Canada and Europe since 2003. Juvéderm® Ultra and Juvéderm® Ultra Plus were approved by the US Food and Drug Administration in June 2006 for the correction of moderate to severe facial wrinkles and folds.

The pivotal trial that led to FDA approval of Juvéderm® Ultra and Juvéderm® Ultra Plus was a multicenter, double-blinded, randomized study that compared the safety and effectiveness of three different types of Juvéderm® dermal filler versus cross-linked bovine collagen filler. The types of HA soft tissue fillers injected were Juvéderm® Ultra, Juvéderm® Ultra Plus, and Juvéderm® 30, of which only the first two have been cleared by the FDA. The study treated the nasolabial folds of 439 subjects. The subjects were randomized to receive one of three types of Juvéderm® soft tissue filler in one nasolabial fold and bovine collagen in the other nasolabial fold. The study demonstrated that 24 weeks after the last treatment, the side treated with all Juvéderm® soft tissue fillers presented longer lasting clinical corrections than the side treated with cross-linked collagen filler. In addition, the volumes required for collagen were higher (median, 2.0 mL) than HA soft tissue fillers (median, 1.6 mL). Adverse events did not differ between any filler type. The preferred filler by the patients was Juvéderm® Ultra, followed by Juvéderm® Ultra Plus.[8]

Other studies compared HA Juvéderm® fillers and bovine collagen fillers.[13,14] The results were similar to the previous study described above. They also showed superior longevity of the HA Juvéderm® fillers compared to bovine collagen fillers. The injection volume for HA soft tissue fillers proved to be lower compared with bovine collagen filler, leading to an additional advantage for the patient in treatment comfort and costs.[15] Both the bovine collagen filler and the Juvéderm® products exhibit perfectly adequate and comparable safety profiles. Adverse reactions were similar for all fillers, and

were mild in severity and short in duration. Juvéderm® Ultra Plus showed longer lasting clinical results than Juvéderm® Ultra.[8,13–15]

The difference between Juvéderm® Ultra and Juvéderm® Ultra Plus, is that the latter has a higher percentage (11%) of cross-linked HA, which makes Ultra Plus more viscous.[8,15] Among the most commonly used FDA approved HA soft tissue fillers, Juvéderm® has a greater HA concentration (24 mg/mL), higher degree of cross-linking to BDDE, and lower G prime, as shown in Table 1.

Juvéderm® has a higher degree of cross-linking among the most frequently used HA dermal fillers. A higher degree of cross-linking may create a more effective physical and chemical barrier to hyaluronidases and free radicals, activity, thereby limiting access to its substrate, and consequently increasing the longevity of the product.[4,16] In 2011, Goodman et al[17] published a prospective, randomized, single blind, split-face study comparing a single administration of Juvéderm® Ultra Plus versus Perlane® in the correction of nasolabial folds over a period of 12 months. The study showed that Juvéderm® Ultra Plus presented a greater longevity, in the maintenance of this clinically relevant correction, than Perlane® at 6, 9, and 12 months after the procedure.[17] Corroborating with this study, an in vitro study, conducted by Sall and Ferard, demonstrated that Perlane® was hydrolyzed by hyaluronidase at a significantly greater rate than the Juvéderm® gel.[16] Not only the degree of cross-linking but also the method of cross-linking may play a role in the longevity of the product.

In 2010, Juvéderm® Ultra with 0.3% lidocaine (Juvéderm® Ultra XC) and Juvéderm® Ultra Plus with 0.3% lidocaine (Juvéderm® Ultra Plus XC) were approved by the FDA. One of the reasons that these products became available in the market was to provide a more comfortable injection experience without spending the extra time in the physician's office, in order to add lidocaine to the free lidocaine version, or to perform a nerve block. Regarding the physical properties, the manufacturer of Juvéderm® Plus XC and Juvéderm® Ultra Plus XC claims that these products present the same characteristics as their respective lidocaine free versions (see Table 1).

Hyaluronic acid dermal fillers with lidocaine

One of the main concerns of patients about filler injections is pain and discomfort, especially for the first time patient. In order to reduce pain and distress, topical anesthetics (such as 4% lidocaine or 7% lidocaine with 7% tetracaine), nerve blocks, and/or incorporation of lidocaine to the filler, have been applied. Topical anesthetics alone can provide adequate anesthesia for some patients, especially with limited treatment into areas that are not so sensitive, such as the nasolabial folds. On the other hand, lip or cheek augmentations for example are more painful. Consequently, the association of a locally injected anesthesia is useful, allowing patients to undergo filler injection with reduced pain and discomfort. Although anesthetic nerve blocks are effective for anesthesia, they may distort the area to be treated, as well as lengthen and complicate the procedure. In addition, many doctors are unfamiliar with performing nerve blocks.[18,19] Consequently, a number of physicians routinely add lidocaine solution to the available fillers, such as HA filler, Radiesse® (Merz Aesthetics Inc) and Sculptra® (Valeant Aesthetics, West Laval, QC, Canada), in order to avoid injectable anesthesia. As previously asserted, some HA dermal fillers are manufactured with 0.3% lidocaine by their makers. The hyaluronic acid dermal fillers manufactured with 0.3% lidocaine approved by the FDA are listed in Table 2.

Studies and the authors' experience have shown that the incorporation of lidocaine to HA fillers significantly reduces pain and discomfort.[18,20–22] Furthermore, returning to the previously injected area for optimal results frequently causes no more pain. It appears that the reduction and/or the absence of pain during the procedure may contribute to the injection of the lidocaine version versus the lidocaine free version being perceived as easier to perform by some injectors. Levy et al demonstrated that the lidocaine version provides superior comfort not only during the injection, but also while massaging, sculpting and after the injection compared to the HA free lidocaine version, when assessed by both injectors and participants.[20]

Despite all the benefits mentioned above, one of the dilemmas about the addition of lidocaine solution is the possible alteration of the physical characteristics of the

Table 2 FDA-approved hyaluronic acid dermal fillers manufactured with 0.3% lidocaine

With 0.3% lidocaine	Company
Restylane-L®	Medicis
Perlane-L®	Medicis
Juvéderm® Ultra XC	Allergan
Juvéderm® Ultra Plus XC	Allergan
Prevelle® Silk	Mentor
Hydrelle™	Coapt Systems Inc

Note: Company locations are as follows: Medicis Aesthetics, Scottsdale, AZ, USA; Allergan, Inc, Irvine, CA, USA; Mentor, Santa Barbara, CA, USA; Coapt Systems, Palo Alto, CA, USA.
Abbreviation: FDA, Food and Drug Administration.

product. This change may negatively impact the efficacy and/or duration of the filler. There may be a difference between a physician adding an aqueous solution into a lidocaine free version dermal filler supplied by the manufacturer and the manufactured pre-incorporated lidocaine version (such as Juvéderm® Ultra XC and Juvéderm® Ultra Plus XC) (see Table 2). An aqueous solution might dilute the product creating less correction per mL changing the product's viscosity and consequently the "lifting" ability. Also, this dilution could reduce the product duration. On the other hand, the addition of lidocaine by the manufacturer appears to have averted these problems. The lidocaine is added during the manufacturing process as a dry/ powder substance and therefore does not dilute or increase the volume of the soft tissue filler.[18]

Another concern, besides the reduction of the efficacy and/or durability of adding lidocaine to dermal fillers, is the possibility that patients may have an allergic reaction to lidocaine. The molecular structure of all local anesthetics consists of three components: tertiary amine, lipophilic aromatic ring, and intermediate ester or amide linkage.[23] Allergic contact reactions to the ester group of anesthetics are common. These reactions are related to the metabolism of the local anesthetics with para-amino-benzoic acid (PABA) and the ubiquitous presence of PABA throughout the pharmaceutical and cosmetic industries. However, reactions to amide anesthetics, including lidocaine, are rare.[24–27] The incidence of true Immunoglobulin E-mediated lidocaine allergy remains uncertain and is presumed to be very low. A review of the literature published in 2012 showed that the incidence of true allergic reaction to local anesthetic agents (including lidocaine and other products) was <1% (0.97%).[28] The majority of documented cases of allergy to lidocaine has been attributed to preservatives (such as methylparaben) present in the vials of lidocaine rather than to lidocaine.[25–28] Juvéderm® family uses a preservative-free powder lidocaine formulation.[18]

A few studies have been published comparing the clinical efficacy, safety and durability of the HA soft tissue fillers manufactured with and without lidocaine. We will discuss some of these articles below, focusing on the Juvéderm® XC. The articles that compared Juvéderm® XC with HA soft tissue fillers manufactured without lidocaine are shown in Table 3.

Efficacy and safety of the Juvéderm® XC

In 2009, Levy et al published a prospective, split-face, single-blind (patients were blinded) study comparing the comfort and ease of injection of a lidocaine-free version HA dermal filler (Restylane-Perlane®) and a hyaluronic acid soft tissue filler manufactured with lidocaine (Juvéderm® Ultra) into the nasolabial fold of 126 subjects (see Table 3). Both treatments required a similar volume of HA soft tissue filler to achieve an equivalent efficacy, were well tolerated, and injection-site reactions were mild and transient in most cases. However, the authors reported more injection-site reactions in the lidocaine free version side of the face, primarily related to a higher incidence of swelling following the procedure.[20]

The same authors, performed another prospective, split-face study comparing the comfort and ease of injection of a HA filler without lidocaine and a HA filler with pre-incorporated lidocaine into the nasolabial fold (see Table 3). Different from the aforementioned study, this study was double-blinded and compared Juvéderm® Ultra lidocaine-free version and Juvéderm® Ultra lidocaine version. Once again, an equivalent volume of both treatments was used to achieve a similar outcome, but in this study both HA dermal fillers presented a similar severity and frequency of adverse reactions. All were localized, the majority were mild to moderate in severity, did not require intervention, and lasted up to 5 days.[18]

Juvéderm® Ultra and Juvéderm® Ultra XC were also compared in another double-blind, split-face study as shown in Table 3. Weinkle et al evaluated their safety and effectiveness.

Table 3 Articles comparing Juvéderm® XC versus hyaluronic acid dermal fillers manufactured without lidocaine

Authors	Journal	n	HA dermal fillers compared	Safety	Efficacy	Longevity
Levy et al[18,20]	*Journal of Cosmetic and Laser Therapy*	126	Restylane-Perlane® X Juvéderm® Ultra XC	Similar	Similar	Not studied
Levy et al[18,20]	*Dermatologic Surgery*	60	Juvéderm® Ultra X Juvéderm® Ultra XC	Similar	Similar	Not studied
Weinkle et al[22]	*Journal of Cosmetic Dermatology*	72	Juvéderm® Ultra X Juvéderm® Ultra XC	Similar	Similar	Not studied
Prager et al[9]	*Dermatologic Surgery*	20	Belotero® X Juvéderm® Ultra XC	Similar	Similar	Similar*

Note: *except for 4-week evenness results.

Both HA dermal fillers had similar safety and effectiveness profiles.[22]

All the studies above showed that Juvéderm® XC is effective in reducing procedural pain during correction of facial wrinkles and folds while maintaining a similar safety and effectiveness profile to HA dermal fillers without lidocaine.[22] The goals of the studies were to compare the level of comfort, safety and effectiveness pertaining to each HA soft tissue filler. Consequently, the follow-ups were short, up to 2 weeks, and durability of the products was not evaluated.

A prospective, split-face, randomized study was recently published by Prager et al (see Table 3). This study is detailed below, but also showed that the safety of Juvéderm® Ultra Plus XC is comparable to other HA dermal fillers manufactured without lidocaine.[9]

Durability of the Juvéderm® XC

As discussed above, Juvéderm® may have an extended longevity, thought to be due to its high concentration of HA and high degree of cross-linking.[8,18] In regards to the lidocaine version of the Juvéderm,® to the best of our knowledge, only one study has compared the duration of effect of Juvéderm® XC and HA dermal fillers manufactured without lidocaine. Prager et al[9] published in 2012 a prospective, split-face, randomized study involving 40 participants, as described in Table 3. The study compared the safety and durability of two lidocaine free HA dermal fillers (Belotero® Balance, Restylane®) and Juvéderm® Ultra Plus XC for the treatment of severe or very severe nasolabial folds. The research had two arms; in one arm 20 patients were treated with Belotero® in one nasolabial fold and Restylane® in the other. In the second arm, 20 patients received Belotero® in one nasolabial fold and Juvéderm® Ultra Plus XC in the other. All the HA fillers presented a similar safety profile. Injections of similar volumes of the three fillers provided equivalent durability at 6, 9, and 12 months follow-up. In the second arm of the study (Belotero® and Juvéderm® Ultra Plus XC), swelling was noted in 25% of the patients treated with Juvéderm® Ultra Plus XC and none with Belotero®.[9] This contrasts with the Levy et al study that showed that the Juvéderm® with lidocaine side presented with less swelling than a HA lidocaine free version, but in this study Juvéderm® was applied instead of Belotero®.[18]

Conclusion

Juvéderm® with pre-incorporated lidocaine is associated with significantly less injection pain than a non lidocaine HA gel formulation. Lidocaine enhanced treatment comfort and optimized the injection experience while maintaining a similar safety and effectiveness profile to HA dermal fillers without lidocaine. Although one split-face, randomized study showed that the durability of Juvéderm® XC is equivalent to other lidocaine free versions of HA products at 6, 9, and 12 months follow-up,[9] it is likely that further studies are necessary to document that there is no difference in duration between the lidocaine versions and the lidocaine-free versions of HA.

Disclosure

The authors report no conflicts of interest in this work.

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