

Durability of Three Different Types of Hyaluronic Acid Fillers in Skin: Are There Differences Among Biphasic, Monophasic Monodensified, and Monophasic Polydensified Products?

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Abstract

Background: Hyaluronic acid fillers are used for facial rejuvenation and are classified as non-cross-linked or cross-linked (monophasic mono- or polydensified).

Objectives: To histologically assess the intradermal durability of three types of fillers (biphasic, monophasic monodensified, and monophasic polydensified), to compare the durability of the products over 6 months, and to evaluate the structural changes after application.

Methods: In all, 25 volunteers received injections of three different fillers in the dermis of the right lumbar region (in one line), and equal amounts of the fillers were injected into three different sites (in the same column), yielding nine points of application in each patient. Each line was biopsied on days 2, 92, and 184; these skin samples were analyzed histologically, and the presence or absence of these fillers was verified by a dermatopathologist.

Results: The histological analysis showed that over 182 days, the amount of the injected monophasic polydensified, monophasic monodensified, and biphasic filler products decreased by 62.5%, 25%, and 12.5%, respectively.

Conclusions: The biphasic and monophasic monodensified fillers presented greater intradermal durability than did the monophasic polydensified filler at 6 months after intradermal injection.

Level of Evidence: 2



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Hyaluronic acid (HA), or D-glucuronic acid + (D-N)-acetylglucosamine, is the most abundant glycosaminoglycan in the human body, and 50% of it is located in the dermis.^{1,2} HA is involved in several important biological functions, such as the regulation of cell adhesion and motility, the manipulation of cell differentiation, and cell proliferation.³

As the body ages, HA becomes damaged and degrades.^{4,5} Key factors of this process include the resorption of structural support, the redistribution of facial fat, the action of gravity, hormonal changes, and the influence of environmental factors such as smoking and sun exposure.^{5,6}

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The application of dermal fillers is becoming an increasingly popular technique for facial rejuvenation.⁷⁻⁹ This procedure is relatively noninvasive and provides excellent three-dimensional restoration of facial volume, rebalances facial proportions and symmetry, and reduces fine lines and wrinkles.^{7,8,10}

In addition to surgical treatments, injectable dermal fillers have been used over the past 20 years to achieve aesthetic goals.¹¹ Siloxane, a synthetic silicone, was one of the first fillers to be used for permanent results,¹² and this compound was followed by bovine collagen fillers.¹⁰ Subsequently, an HA-based filler was launched because of its characteristics, including its biocompatibility, non-teratogenicity, sterility, chemical inertness, safety, durability, stability, reversibility, ease of application, and good cost/benefit ratio; in addition, this filler was non-migratory or non-modifying based on tension or organic substances and was approved by sanitary authorities.^{13,14}

HA was originally isolated in 1934, after being extracted from bovine vitreous humor, and it proved to be versatile for therapeutic purposes, such as ocular and orthopedic surgery.^{1,7,12} HA can be of an animal origin, such as that extracted from a cockscomb, or of a non-animal origin, such as that produced by cultures of *Streptococcus* species (eg, *S. pyogenes* and *S. zooepidemicus*).^{1,7,10} HA is highly biocompatible without tissue specificity and is highly hydrophilic.^{5,8,13,15} Thus, it has the ability to immediately fill a volume of approximately 15% at the site of injection.⁸ After injection, an immediate inflammatory process takes place, which fades in 4 to 5 days.^{12,16} Despite the low rate of complications, sometimes a hyaluronidase injection, antibiotics, or steroids may be necessary to treat these side effects.^{16,17}

The fillers based on HA can be classified as non-cross-linked or cross-linked.^{8,18} Cross-links are intermolecular bonds that enhance the stability and durability of clinical implants.^{13,18} Nevertheless, the optimal level of cross-linking should be determined because cross-linking decreases the hygroscopicity and therefore the effectiveness of this filler.^{18,19} The most commonly used cross-linking materials are divinyl sulfone, 1,4-butanediol diglycidyl ether (BDDE) and p-phenylene bisethyl carbodiimide, which have been refined to reduce endotoxins and the risk of sensitivity.¹⁸

Cross-linked fillers are classified as monophasic or biphasic.¹⁹⁻²² Monophasic fillers consist of a homogeneous mixture of high- and low-molecular-weight HA, making their application easier.¹⁹⁻²² Biphasic fillers have cross-linked particles of HA dispersed in a non-cross-linked HA vehicle; therefore, the HA is heterogeneous.¹⁹⁻²² Monophasic fillers may be further categorized as monodensified (cross-linking occurs after homogeneous mixing) or polydensified (cross-linking occurs separately, before the mixture is produced).¹⁹⁻²²

There has been some commercial interest in classifying all HA fillers as the same, as if they are all made from

the same material.²³ However, there are many studies that refute this notion.^{8,13,18-22,24} It is important to note that the physicochemical structures and rheological properties of filler products are critical factors of their clinical performance.¹⁹

Among the rheological properties, the most important are the viscosity complex and elastic module/modulus (G).^{1,2,19} The viscosity complex relates to the way the filler flows from the needle and therefore its ability to resist the fluid phase of shearing forces. In contrast, G is related to its ability to resist deformation while being injected.^{2,19} A gel with a greater elastic component will be firmer and stronger and will undergo fewer changes in shape when pressure is applied. Clinically, this type of gel will have a greater ability to generate volume and support.¹

Finally, because there is not a single manuscript in the literature evaluating the long-term intradermal durability of the three different types of manufactured HA fillers (ie, biphasic, monophasic monodensified, and monophasic polydensified), our study compares the histology and the durability of a representative HA filler from each of these three classes over 6 months. Thus, this is the first clinical report published specifically in this field.

METHODS

This was a phase IV, single-center, prospective, open, observational clinical trial involving 25 female subjects between 45 and 60 years of age with skin types I to VI (Fitzpatrick classification). This study was conducted from December 2011 to January 2014. All subjects were recruited from a private clinic's patient log list in the city of Campinas, SP, Brazil; based on the Brazilian rules for clinical trials, the subjects were reimbursed for transportation and meals.

In general, the exclusion criteria were diseases related to the connective tissue, systemic uncontrolled diseases, pregnancy or breastfeeding, a history of any adverse reactions to the fillers, medicines that interfered with coagulation, and conditions that could interfere with the evaluation of the results.

This study was approved by the independent ethics committee of the University of Sao Francisco (Bragança Paulista, SP, Brazil; Project Number: 0597.0.142.000-11), and all patients signed an informed consent form before joining the study. This study also complied with all principles of the Declaration of Helsinki, Good Clinical Practices, the International Conference of Harmonization, and local regulatory requirements.

All HA filler injections and skin biopsies were performed by the principal investigator of this clinical trial, who is also the first author of this manuscript. After successful aseptic and antiseptic procedures were performed on the right lumbar region of the subject in the prone position, a local

anesthetic was applied (Xylocaine with epinephrine 1 : 200,000, AstraZeneca Inc., Mississauga, Canada).

Using a bolus technique with a vertical dermal puncture, we performed three applications of 0.2 mL of Product 1 (biphasic—Perfectha Derm; 20 mg/mL; ObvieLine, Dardilly, France), three applications of 0.2 mL of Product 2 (monophasic monodensified—Teosyal Global Action; 25 mg/mL; Teoxane, Paris, France), and three applications of 0.2 mL of Product 3 (monophasic polydensified—Esthelis Basic; 22.5 mg/mL, Anteis, Loney, Switzerland).

It is important to disclose that the average epidermal thickness is 0.0837 mm (epidermis plus dermis).²⁵ The thickness of dermis on the back can vary from 0.90 mm (Fitzpatrick phototype II) to 1.87 mm (Fitzpatrick phototype VI).²⁶ Dermis is considered to have a superficial, medium or deep depth in relation to surface at thicknesses of up to 0.3 mm, between 0.3 and 0.7 mm, and greater than 0.7 mm, respectively.²⁷ In this study, the HA fillers were injected at a depth of 0.7 mm, into the middle dermis.

All HA fillers used in this study were injected with needles of the same length and gauge (30G* ½). However, to ensure that all injections were performed at a depth of exactly 0.7 mm depth, several sterile stop-penetration devices were constructed by cutting the plastic cap of a 30G* ½ needle (BD 30G ½ Precision Glide Needle, Becton & Dickinson & Co., Franklin Lakes, NJ), which allowed only 0.7 mm of the needle to penetrate the skin, in a similar manner as has previously been described in the literature.²⁸ Such devices were locked over their needles after they'd been connected to the syringe, as shown in Figure 1.

The same filler was applied in three different sites in the same column, leading to a total of nine application points on the right lumbar area (Figure 2). The punctures were made equidistant from each other, with 1.5 cm between lines (vertical distribution) and 1.5 cm between columns (horizontal distribution). Injection points were marked at 0.3 mm on the right side with permanent black ink (Sharpie Permanent Marker Black; Newell Brands Inc., Atlanta, GA), to denote where biopsies should be performed. All ink marks were refreshed on D2 and D32, and patients

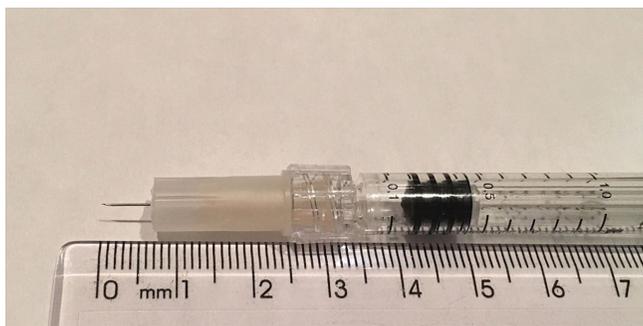


Figure 1. Standardization of needle injection depth.

were asked not to scrub that area when showering; in case any mark began to fade, patients were instructed to return to the clinical site for the mark to be refreshed.

On day 2 (D2), D92, and D182 after the injections, skin biopsies were performed at each horizontal line using a number three punch, and a small cylinder of skin was removed. There was no need for sutures because the fragment removed was very small and the aesthetic result is better with healing by secondary intention. The skin samples were prepared for histology (4-micron-thick sections) and stained with Alcian blue to analyze the features of the intradermal histological durability of the different HA-based commercial fillers. The histological slides were reviewed by an author (P.R.G.O), a surgeon and dermatopathologist with experience in evaluating skin specimens collected by dermatologists and plastic surgeons. This individual evaluated each one of the slides without knowing the day the specimen was collected (D2, D92, or D182) or the product that had been injected. The evaluation was based on a subjective determination of the “presence” (+) or “absence” (–) of HA islets. The histological analysis was the same as has been used in other traditional studies of cosmetic fillers.^{7,15,19,21,29}

The mean distribution of these sample would be normal,²⁴ regardless of the distribution of the studied variables, thereby allowing the use of parametric techniques. Before the analysis, the normality of the data was tested using the Anderson-Darling test. Analysis of variance with two factors (intra- and inter-treatment), supplemented by the Scheffe test, were used to compare the variables of both groups that fit the normal distribution. Differences among categorical variables were assessed by nonparametric analysis of variance (Kruskal-Wallis and/or Mann-Whitney Test). The same tests were used only if the data did not adhere to the normal distribution (bell curve/Gaussian curve). The McNemar test was used to perform a comparative analysis of the products. To compare the outcomes of the products and time points, Fisher's exact test was used. The level of significance was 5%. SAS software, version 9.3 (SAS Institute Inc., Cary, NC), was used to perform the statistical analyses.

RESULTS

Twenty-four out of twenty-five female subjects (96%) completed the clinical trial. One subject withdrew from the study one day after the first filler injection because she decided not to undergo the skin biopsies. As such, the statistical analyses were performed based on the 24 final subjects with a mean age of 53 ± 3.87 years (range, 46-60 years). The group comprised 13 phototype II subjects, 7 phototype III subjects, and 4 phototype IV subjects (Table 1).

After the application of the three types of HA-based fillers, biopsies were performed on three different occasions,

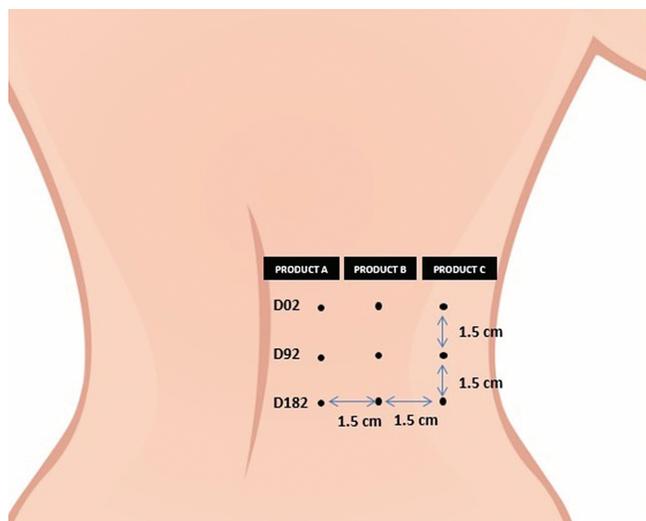


Figure 2. Schematic illustration of the standardization of product injection in the right lumbar area.

D2, D92, and D182 (Figure 3). The number of positive biopsies is shown in Table 1 and Table 2. Positivity was based on the presence or absence of HA islets as analyzed histologically.

Analyzing the positive biopsies, the histology showed that the amounts of Products 1, 2, and 3 found on D2 in the biopsies were similar; the presence of all three fillers in all 24 patients was verified. On D92, major differences between the amounts of the fillers remaining were found: Product 1 was still present in 22 patients, Product 2 was still in 20 patients, and Product 3 was still in 16 patients. On D182, even greater differences between the amounts were observed. Product 1 was present in 21 patients, whereas Products 2 and 3 were present in 18 and 9 patients, respectively. After 182 days, the injected amount of Product 3 was reduced by 62.5%, whereas Products 2 and 1 were reduced by 25% and 12.5%, respectively (Table 2). Thus, Product 1 had the highest dermal durability.

Table 3 shows the histological behavior of the three different fillers over the course of 182 days. The amount of Product 1 did not change during the study ($P > .05$, in all binomial date comparisons). The amount of Product 2 decreased on D92 compared to D2 ($P = .0455$), but it did not change from D92 to D182 ($P = .1573$). Finally, Product 3 exhibited a significant, progressive reduction from the first two-date comparison (D92 vs D2, $P = .0047$) to the end of the study (D92 vs D82, $P = .0001$).

As shown in Table 4, both Product 1 and monophasic, monodensified Product 2 exhibited the exact same histological pattern of durability based on a visit-to-visit comparison ($P > .05$). However, Product 2 was histologically similar to Product 3 until D92 ($P = .3177$), but was more abundant than Product 3 on D182 ($P = .0189$).

DISCUSSION

Tissue mobility is one of the most important aspects when studying the longevity of HA fillers because more frequent corrections need to be made in areas with more movement.³⁰

Another factor of filler durability is the anatomical location. Indeed, the location where a filler is placed is defined by the characteristics of the filler material and the type of correction intended.³¹ The differences in skin thickness among facial cosmetic units widely vary and can range³² from 1.04 to 1.86 mm.³³ However, even when “dermal” HA fillers are injected to improve nasolabial fold (NLF) depth, the histological presence of HA fillers is observed in the hypodermis, and some material can be found in the deep dermis of 56.25% of patients; HA fillers remain in the more superficial dermis in only 6.25% of patients.³³ As such, and because each patient would be submitted to three biopsies for each filler, for a total of nine biopsies in an area of 9 cm², it was decided that all injections should be performed in the lumbar area in this study.

The durability of an HA filler is also determined by whether the HA filler is cross-linked. Non-cross-linked HA fillers, or non-stabilized HA fillers, as they are also called, last less than 24 hours in the skin.^{30,34} Traditionally, biphasic cross-linked fillers remain for 6 to 8 months after treatment.^{15,34,35} With this well-established scientific concept in mind, physicians consider cross-linked HA fillers as “heavier” injectables,³² and they are the most common fillers used worldwide.³⁶ This was the reason why we decided to compare the durability in skin of these three different types of manufactured HA fillers that are commercially available in most countries.”

Some differences among different HA fillers have been published in the literature. A split-face clinical trial evaluated the durability of two different BDDE-based HA fillers in NLFs: a 24 mg/dL monophasic, monodensified product and a 20 mg/dL biphasic product.¹¹ In the follow-up examinations from 6 to 12 months after injection, the product with the higher concentration clearly exhibited greater longevity than the product with the lower concentration. This greater apparent long-term durability of the more concentrated product may have been related to its distinct physiochemical properties, affording it a greater relative resistance to enzymatic and/or free radical degradation in the dermis.¹¹ Our histological findings may clarify those possibilities by showing that in fact, biphasic and monophasic monodensified fillers do not differ in terms of histology.

According to the biological behavior of HA fillers, biphasic fillers are present in large deposits and reach deeper levels of the reticular dermis.⁷ Conversely, monophasic monodensified fillers show a tapered layer distribution in the reticular dermis,⁷ whereas monophasic polydensified products spread throughout the dermis in a diffuse manner, without reaching the papillary dermis.^{7,37} These

Table 1. Demographic Data of the Subjects who Completed the Study and Histological Analysis of the Skin Biopsies of Each Product and Study Visit ($n = 24$)

Subject Information			D2			D92			D182		
#	Age (years)	Phototype	Product 1	Product 2	Product 3	Product 1	Product 2	Product 3	Product 1	Product 2	Product 3
1	58	II	+	+	+	+	+	+	+	+	+
2	49	II	+	+	+	-	-	-	-	-	-
3	54	II	+	+	+	-	-	-	-	-	-
4	54	II	+	+	+	+	-	-	+	-	-
5	59	II	+	+	+	+	+	+	+	+	+
6	51	III	+	+	+	+	+	+	+	+	-
7	56	II	+	+	+	+	+	-	+	+	-
8	50	II	+	+	+	+	-	+	+	-	+
9	55	II	+	+	+	+	+	+	+	+	-
10	54	III	+	+	+	+	+	-	+	-	-
11	54	III	+	+	+	+	+	+	+	+	-
12	48	IV	+	+	+	+	+	+	+	+	+
13	48	III	+	+	+	+	+	+	+	+	+
14	53	IV	+	+	+	+	+	+	-	+	+
15	51	III	+	+	+	+	+	+	+	-	-
16	51	IV	+	+	+	+	+	-	+	+	-
17	53	IV	+	+	+	+	+	+	+	+	+
18	46	III	+	+	+	+	+	+	+	+	-
19	52	II	+	+	+	+	+	+	+	+	+
20	53	III	+	+	+	+	+	-	+	+	-
21	56	II	+	+	+	+	+	-	+	+	-
22	59	II	+	+	+	+	+	+	+	+	+
23	60	II	+	+	+	+	+	+	+	+	-
24	47	II	+	+	+	+	+	+	+	+	-

+, presence of HA islets; -, absence of HA islets.

findings lead to the conclusion that the different cross-linked HA-based fillers have predictable patterns and characteristic distributions in the dermis, which are consistent after 2 weeks.⁷ Based on these findings, it is possible that the deeper the filler penetrates, the longer it lasts.

Apparently, cross-linking, viscoelasticity properties, and diffuse distribution determine the longevity of these fillers.^{7,37} Among fillers that have been shown to be safe with low immune responses and remain intact in the skin,³⁷ the durability of HA fillers seems to be inversely proportional to the homogeneity of the distribution. In this clinical trial, we observed that filler depth is not the key feature of a product; the biphasic (deepest)⁷ and monophasic monodensified products lasted longer than the monophasic polydensified product, which had a distribution similar to that of the monodensified product.⁷ Most likely, cross-linking and viscoelasticity are more important factors.

The superficial placement of biphasic products has already been described as associated with tenderness and an eosinophilic inflammatory infiltrate in the dermis.²² The rheological profiles of HA fillers can vary according to the manufacturing method used.²⁰ However, we do not believe our findings suggest that monophasic fillers are better for use in fine lines and wrinkles than biphasic fillers, or vice versa. We believe that the concentration of HA in a filler product should determine its specific use, which is in accordance with the commercially available products in this category. Once commercial brands of biphasic, monophasic monodensified, or monophasic polydensified fillers have products with lower concentrations of HA, they may be indicated for use in areas with superficial or thin dermis.

Independent of HA cross-linking and concentration, all fillers undergo rheological changes after passing through

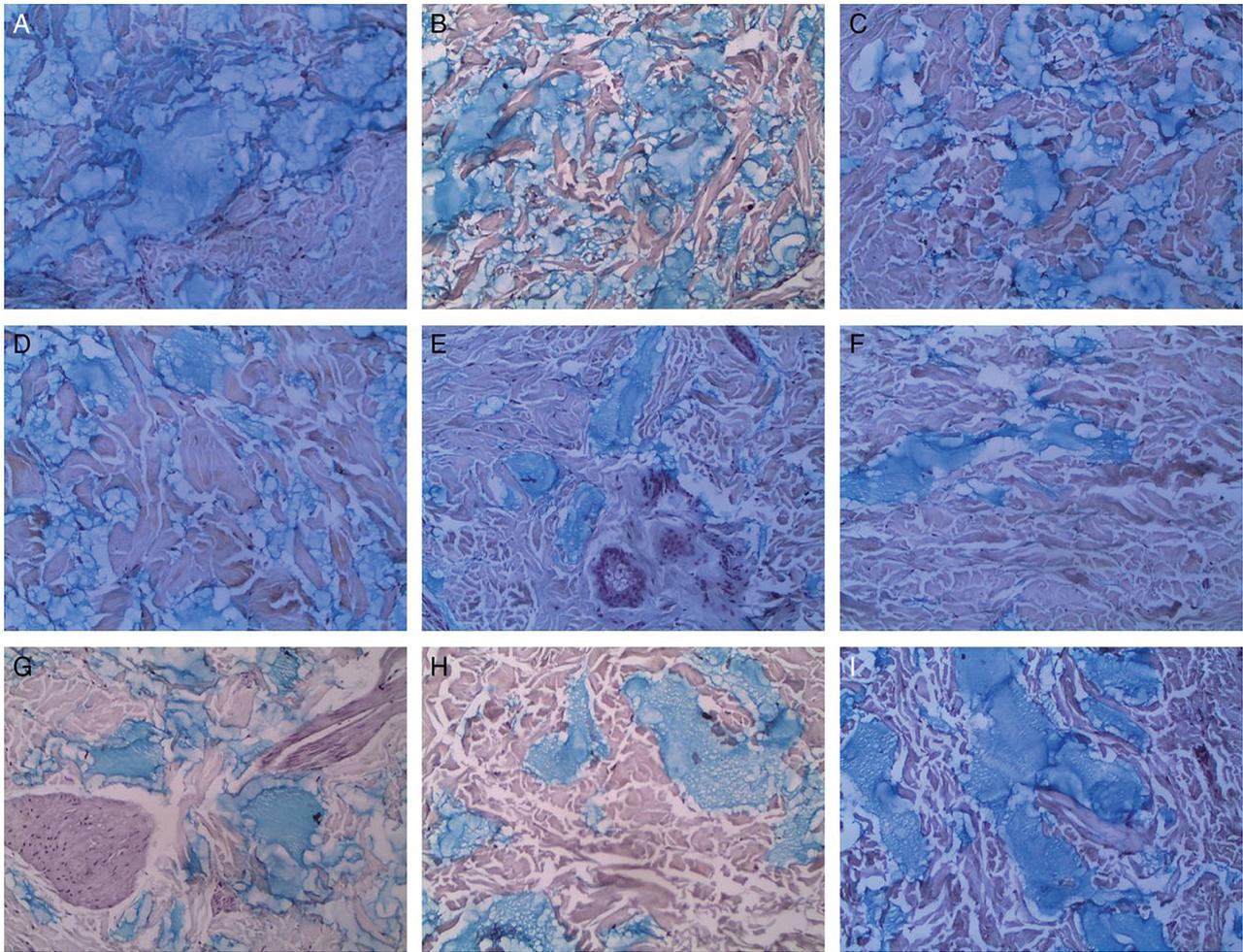


Figure 3. Slides of biopsy specimens from a 56-year-old female subject. The amount of the filler and the subsequent degradation over time are represented by Alcian blue staining ($\times 100$ magnification). (A) Product 1 at D2, (B) Product 1 at D92 (C) Product 1 at D182, (D) Product 2 at D2, (E) Product 2 at D92, (F) Product 2 at D182, (G) Product 3 at D2, (H) Product 3 at D92, and (I) Product 3 at D182.

Table 2. Number of Patients in Whom the Fillers Were Present in the Biopsies Over Time and the Percentage of Filler Reduction by the End of the Study ($n = 24$)

Product	D02	D92	D182	Reduction (%)
Product 1	24	22	21	12.5
Product 2	24	20	18	25
Product 3	24	16	09	62.5

Table 3. Evaluation of *P*-Values Comparing the Presence of Fillers in the Biopsies Between Two Different Visits for the Same Product ($n = 24$)

Product	D92 \times D02	D182 \times D92	D182 \times D02
Product 1	0.1573	0.3173	0.0833
Product 2	0.0455*	0.1573	0.0143*
Product 3	0.0047*	0.0082*	0.0001*

* $P < .05$.

needles.²⁰ These changes are intensified when the acid comes into contact with endogenous hyaluronidase, which can interfere with the behavior of the material once it reaches deep tissue.²⁰ Biphasic fillers show more rheological stability than monophasic fillers.²⁰ This finding may be correlated to biphasic fillers' superior durability, lower

propensity to be homogeneously distributed throughout the injected area, and greater ability to withstand the compressive forces of passing through a needle,^{7,20,37} which together, produce the clinically long-lasting results of biphasic products.^{20,38} We strongly believe that the findings reported in these in vitro rheological studies explain

Table 4. Evaluation of *P*-Values Comparing the Presence of Fillers in Biopsies Between Two Products in the Same Visit (*n* = 24)

	Product 2 D92	Product 2 D182	Product 3 D92	Product 3 D182
Product 1 D92	0.6662	0.2448	0.0330*	<0.0001*
Product 1 D182	0.2921	0.4614	0.0860	0.0003*
Product 2 D92			0.3177	0.0027*
Product 2 D182			0.7516	0.0189*

**P* < .05.

the histological durability of the biphasic and monophasic monodensified products that we observed.

Monophasic fillers are the newest type of HA fillers. Some authors believe that the visual clinical effect, safety and durability of the injection of both biphasic and monophasic products in NLFs are equivalent.^{39,40} There is a good argument that any HA-based filler is inherently more desirable than products not based on degradable substances or even nonhuman animal fillers.

A good example of a non-degradable filler is any product with calcium hydroxyapatite (CaHA). Although CaHA is superior in that it can achieve results lasting from 18 to 24 months,⁴¹ HA is still the preferable injectable filler.⁴² Similarly, even animal-based products, such as porcine or bovine collagen, can be used as aesthetic fillers;^{34,43} porcine collagen is less allergenic than bovine collagen,⁴³ and both have good durability and efficacy.³⁴ Because of these features, these fillers should be considered alternatives to HA fillers,⁴³ and we vehemently suggest that HA-based fillers should be the first choice for aesthetic purposes.

Manufacturing characteristics are not the only factors to consider when selecting the best fillers for patients. In fact, the careful selection of patients, fillers, and techniques would maximize patient satisfaction.^{9,17} The choice of product should be guided by the zone in which the product will be injected, the characteristics of the tissue, the volume of the product used, and the required time for the material to last.^{44,45}

HA fillers have many advantages, such as biocompatibility, non-immunogenicity, water-bonding properties,

Table 5. Nonanimal HA Fillers Used in This Clinical Trial and Examples of Corresponding HA Fillers With Concentrations Ranging From 20 to 25 Mg/G Approved for Commercial use in the United States^{18,20,29,46-49}

Category of HA Filler	HA Used in This Clinical Trial	Example of a Commercial Brand Available in the United States
Biphasic	Perfectha Derm (20 mg/mL; ObvieLine, Dardilly, France)	Restylane (20 mg/mL; Galderma Laboratories, L.P., Dallas, TX)
Monophasic monodensified	Teosyal Global Action (25 mg/mL; Teoxane, Paris, France)	Juvéderm (24 mg/mL; Allergan, Inc., Irvine, CA)
Monophasic polydensified	Esthelis Basic (22.5 mg/mL; Anteis, Lonay, Switzerland)	Belotero (22.5 mg/mL; Merz Aesthetics, Inc., San Mateo, CA)

Other HA non-animal fillers approved by the FDA⁴⁶ such as Prevelle Silk (4.5-6.0 mg/mL of HA;⁴⁸ Genzyme Biosurgery, Cambridge, MA), Elevess (28.0 mg/mL of HA;⁵⁰ Anika Therapeutics, Inc., Woburn, MA), or Captique (4.5-6.0 mg/mL of HA;⁴⁸ Genzyme Biosurgery, Cambridge, MA) were not included in this table because their concentration did not fall within the given range or they had not yet been commercialized in the United States. Furthermore, no specific mention was found for these fillers about their cross-linking category (ie, biphasic, monophasic monodensified, or monophasic polydensified).

and biological functionality.⁴⁶ Undoubtedly, these features allow HA fillers to be used in the third most common minimally invasive cosmetic procedure performed by plastic surgeons in the United States.⁴² HA fillers are the focus of aesthetic companies around the world that are launching new products using new marketing concepts, which are not always clearly understood by prescribers. This manuscript intends to help physicians to: (1) have a comprehensive review of the differences among biphasic, monophasic monodensified, and monophasic polydensified fillers; (2) know that the manufacturing process of these three categories of HA fillers directly impact the durability of the filler in the skin; (3) know that biphasic HA fillers have the best durability; and (4) better differentiate the best HA filler for their patients based on several factors, including cost-benefit aspects. Indeed, this is the first histological study to evaluate the durability in humans of one representative HA filler from each category.

Ideally, all representatives of the same category would be evaluated in the same subjects to understand whether there is a range of durability within the same category, based on the manufacturer and its standard procedures. However, because vast number of these medical treatments available around world is a limiting factor, in addition to the prohibitive number of skin biopsies that would be performed on the same patient; this is particularly true in countries where patients cannot be financially compensated, such as in Brazil.

As such an ideal study is not yet possible yet, the best approach is to create a link between the results obtained here with other commercially available representatives

from the same categories. Thus, a product comparison table of fillers available on the US market and those used in this clinical trial has been included in this manuscript. This information will definitively help readers of the *Aesthetic Surgery Journal* to better create a parallel between the results obtained in this clinical trial and their clinical reality, assisting them in selecting the best product for their patients (Table 5)

CONCLUSIONS

The amounts of biphasic, monophasic monodensified, and monophasic polydensified fillers decreased by 12.5%, 25%, and 62.5%, respectively, over a period of 182 days after injection. Comparing D92 vs D02, D182 vs D92, and D182 vs D02, the reduction in the histological presence of the biphasic product was not statistically significant over 6 months. Interestingly, the histological presence of the biphasic and monophasic monodensified fillers was statistically similar throughout the trial. Furthermore, the amount of monophasic polydensified filler was equal to that of the monophasic monodensified filler at three months after injection, but the amount of monophasic monodensified filler remaining after six months exceeded that of the monophasic polydensified filler. In summary, the durability of the dermal biphasic HA-based filler was similar to that of the monophasic monodensified filler, both of which were superior to the monophasic polydensified filler.

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Disclosures

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