

Dermal Fillers and Combinations of Fillers for Facial Rejuvenation

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KEYWORDS

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Until recently, the use of dermal fillers was limited in the United States by the small number of products approved by the Food and Drug Administration (FDA). This limitation mandated that combinations of fillers frequently married an older technology, such as a human or bovine-derived collagen, with a newer product, such as a tightly cross-linked hyaluronic acid (HA). Although this methodology had its proponents who espoused the benefits of the lidocaine found in the collagens or the structure provided by collagen fibrils, the sheer lack of data combined with the want of results spelled the demise of these combinations. More recently, the products approved for use in the United States have opened up the range of possibilities for combinations of products that are synergistic in their effects. Combinations of products may be discussed in temporal or anatomic relationships. Temporal combinations refer to the use of different fillers at different times, whereas anatomic combinations refer to the use of different fillers in different parts of the face. Before discussing how the various fillers may be used in combination, it is worthwhile to consider their use in isolation. Soft-tissue augmentation products under consideration in the present article include the hyaluronic acids, poly L lactic acid (PLLA), calcium hydroxylapatite (CAHA), porcine collagen, and silicone.

HA are the most widely used soft-tissue augmentation products.¹ These molecules are polymers of d-glucuronic and n-acetyl-d-glycosamine, which are then cross-linked for stability following injection. The various products differ in their concentrations of cross-linked HA, degree

of cross linkage, flow characteristics, tissue-lifting ability, and method of particle manufacture. In addition, some products contain lidocaine. The main HA products approved for use in the United States are those of the Restylane, Juvederm, and Prevelle families. Each has unique characteristics that affect their utility for specific indications and each has brand-extension products that will enhance the opportunities for combination treatments.

Collagens presently approved for use in the United States are porcine in nature. Autologous collagen (Isolagen) has not been demonstrated to be safe and effective, whereas bovine and human-derived collagens are not effective enough to warrant continued marketing and distribution. The porcine collagen used in the United States is Evolence, which has a novel ribose cross-linking technology.² This cross-linking is free from the types of chemical structures that appear foreign to the immune system, and thus, it has a longer duration of correction. Evolence is approved for 6 months duration and animal models suggest that this duration could be for as long as 9 to 12 months.³

Evolence is unique in several aspects. Unlike the HA, it is opaque, and thus, is not suitable for placement in the superficial dermis. Because it contains collagen fibers, it is capable of providing some structural support but is less structural than Perlane or Radiesse. Although Evolence is not suited for injections into the lip, a future version (Evolence Breeze) has smaller collagen chains and is approved for use in the lips outside of the United States.

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The most logical uses for Evolence in isolation are to correct moderate depth nasolabial creases and marionette lines. As previously mentioned, its opaque nature make it less than ideal for superficial placement, but it is reasonable to combine it with HA, which can be placed superficially to it. Thus, Evolence may be used to replace volume in the marionette and nasolabial creases and a hyaluronic acid can be used to etch out the lines above the crease.

PLLA is a device capable of stimulating collagen production following its injection. It is suited for volume restoration. Its method of action relies upon stimulation of fibroblasts and other cells to lay down a matrix of collagen and elastic fibers.⁴ Unlike many other devices, PLLA relies upon the physician to determine its ultimate formulation. Because it is a lyophilized powder, there remain many variables in its final concentration. According to the package insert, the recommended amount of water for each bottle is 3 to 5 mL.^{5,6} In addition, the product requires at least 4 hours of time to imbibe water and become saturated. However, many experienced injectors of PLLA believe that leaving it in water for at least 24 hours is ideal. There is also considerable debate about the optimal reconstitution formulation for PLLA. Some advocate the use of 7 mL of water as diluent and others recommend that additional volume in the form of lidocaine be added into the mix. At the present time, there are few well-controlled clinical trials to determine what the optimal dilution or reconstitution formulae are.

Two areas uniquely suited for treatment with PLLA are the temporal and malar regions. As the malar fat pad becomes atrophic and descends, the middle third of the face becomes concave. Several malar grading scales are available to help assess the degree of malar descent and atrophy but the senior author believes that the SOBER scale is the most useful. Injections into these areas should use dilutions of between 7 to 9 mL of fluid per bottle and it is recommended that dilution lasts for at least 24 hours. The addition of 2 mL of lidocaine with 1:100,000 epinephrine to 5 mL of water is helpful in decreasing patients' discomfort.

Injections of PLLA should be made at intervals of not less than 4 weeks, which enables the injector to minimize the risk of overcorrection and of subcutaneous papule formation. A 0.5 inch, 26-gauge needle may be inserted into the deep dermis or into the dermal/subcutaneous junction. It is better to inject PLLA into a deeper plane than a superficial one as the latter will result in the formation of papules. Multiple modalities of injection techniques are

useful when injecting this product. Serial puncture, fanning, and linear threading may all be used to lay down a matrix of product in a deep plane. Because it is a suspended particle, rather than a homogenous solution, it can precipitate in the syringes so it is essential to inject in a rapid manner.

Malar injections should begin with one bottle of PLLA and typically require three or four bottles of product to correct moderate malar atrophy. Once the cheeks have been restored, it is reasonable to correct nasolabial creases, marionette lines, glabella furrows, atrophic lips, and perioral rhytids. None of these is best treated with PLLA. Thus, for many patients, the addition of another product will optimize the outcome. Depending on the anatomy and goals of patients, a hyaluron, collagen, or CAHA can be used to treat the discrete lines and creases. Patients that have fine lines or wrinkles in addition to their volume loss may have their nasolabial creases, marionette lines, or glabella treated with collagen or HA. Deeper folds may be treated with thick HA, such as Perlane, or with CAHA.

The use of CAHA for soft-tissue augmentation has been well documented, especially for use in the midface region.⁷ Radiesse has been safely and effectively used to fill deep creases and to restore lost volume. Its use with other products, such as HA or collagen of different sized particles, is likely to increase in frequency as their utility become studied. Radiesse is of particular use for areas, such as the jaw, where bone resorption has played a dominant role in facial recession. CAHA has been injected in a variety of locations, and to date, there are two areas of the face that should be avoided. One area that should not be injected with CAHA is the vermilion of the lip because of the increased rate of nodule formation in this location. Another area that may be best served by other fillers is the tear trough, where injections may lead to visible nodules that are apparent through the thin skin of this location.

HA products may be combined with each other and with other classes of fillers. There are many different rationales for the combinations, which are primarily based upon their structural and flow characteristics. Juvederm has several attributes that render it very smooth and easily injected. Thus, it is a good candidate for the treatment of the tear troughs and of lip atrophy. Patients that have superficial perioral rhytids may also benefit from Juvederm injections. However, it does not have the lifting or structural qualities of other fillers and may not be suitable for malar injections.

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COMBINATIONS FOR FACIAL REJUVENATION

The most interesting development in the arena of facial rejuvenation is not the advent of any single product or technology but rather the possibilities of combining the various treatments and products in ways heretofore not possible. For instance, addressing midface descent with injections into the malar area can help lift the face, but if there are static perioral lines and the malar fat pad has evaporated, there will not be a symmetry or balance to the face. The ability to use soft products in the lips and perioral areas, firm products for sculpting, volumizers for volume restoration, botulinum toxins in dynamic areas, and lasers and light sources on the surface and mid dermal structures is by far the most significant development in recent history. As we learn more about individual products, we will gain more insights into their use with each other. For now, however, it is useful to have some rational framework to consider which combinations make sense for restoring facial anatomy to a more youthful appearance. In broad terms, we may divide products into those that add volume, those that fill lines, those that provide lift, and those that are able to buttress. There is a broad overlap with product indications and none is limited to one of these categories by either the FDA or their intrinsic properties. However, it is useful to begin to think about fillers in this manner to help devise methodologies that provide optimal outcomes for patients.

VOLUMIZERS WITH FILLERS

Many, if not most, patients that have lost enough volume to benefit from PLLA will also need treatment of lines that have developed. PLLA has an excellent safety and efficacy profile when used for volume restoration. The areas that are still in a state of flux are the proper amount, type of diluent, and timing of reconstitution used. Originally, reconstitution with water was recommended for at least 4 hours before use and with a 3 mL quantity. This has since changed and many injectors are using more water, more time, and adding in lidocaine with 1:100,000 epinephrine. There has not been a definitive clinical trial to support any dilution or methodology, and for now it is reasonable to use 4 mL of water for more than 24 hours to reconstitute the product. Immediately before use, the senior author adds an additional 3 to 4 mL of 1% lidocaine with 1:100,000 epinephrine (if patients have epinephrine sensitivity or are elderly, this may be deleted).

Optimal combinations using volumizers with fillers are ones that address the issues in a coherent manner. Among the most common

are PLLA in the cheeks, lower jaw, and temples, with fillers in the cheeks, marionette, and perioral areas. This strategy offers the core physician the opportunity to demonstrate mastery of facial rejuvenation and offers the patients the benefit of the use of products that excel at specific functions for defined locations.

Many patients lose volume of the malar and temporal areas beginning at approximately 50 years of age. This anatomic shift has been documented by Rohrich and Pessal.⁸ Restoration of the temporal and malar areas may be achieved with PLLA. To begin this process, patients need to have a thorough understanding that treatments with PLLA are a process rather than a discrete procedure and that several injection sessions are planned. As with any procedure, the risks, benefits, and alternatives of this treatment should be discussed. For PLLA, one unique potential adverse event is the formation of subcutaneous papules, with an estimated incidence of approximately 2%.⁹ Injections of PLLA should be made with a 25- or 26-gauge needle that is between 0.5 to 1 in. When administering PLLA to the malar area, the goal should be to lay down a three-dimensional matrix of product that will stimulate collagen production in a uniform manner. However, since one is injecting a particulate product suspended in a liquid medium (rather than a gel) the reality is that despite one's best attempts to place the product homogeneously, its distribution is subject to gravitational, muscular, and thermal forces before it begins its collagen stimulation.

Adding volume to the malar area should begin with one bottle of material injected at the dermal/subcutaneous plane. When injecting, particularly in people with thin skin, it is preferable to err on the side of deep placement rather than superficial. For patients with a concavity, the goal should be restoration of a normal contour with PLLA. A cross-hatching technique (fanning with the needle inserted from the zygomatic arch pointed to the angle of the mouth). It is also advisable to inject the product with some degree of cross hatching to ensure that there is adequate dispersion of the product along the desired plane. Treatments should be spaced at 1-month intervals with approximately three treatments planned before a rest interval of a few weeks is taken to measure the response.

Concomitant with the depletion of malar soft tissue, there is frequent loss of temporal soft tissue. Treatment of this area is also ideally suited to injections with PLLA. These treatments should use one bottle per session for most patients and may be performed at the same time as the malar

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treatments. A 1-inch needle is preferred for this treatment as injections should be performed at the plane just superior to the periosteum (deep to the muscular layer). A linear threading and fanning technique may be used to deposit PLLA in this plane.

PLLA is also being increasingly used to treat the prejowl sulcus. This area is a frequent source of cosmetic concern as the loss of underlying bone and soft tissue depletes the support for the overlying skin and the corners of the mouth. Injections of this area may be approached from the inferior aspect of the ramus. When injecting this location, one must be cautious to avoid the underlying vasculature. A fanning technique may be used to deposit 0.5 cc of PLLA on each side. Over time, as volume is restored, it is possible to attain reshaping of this area to a more youthful appearance. One additional benefit is that by restoring volume here, it is easier to address some of the other concerns that affect the mouth and perioral areas.

Addressing additional stigmata of facial aging may be performed at the same time as volume correction with PLLA. PLLA may help not only to restore youthful contours to the temple, cheeks, and prejowl areas but also the appearance of the skin. Some fine lines that traverse the cheeks will fade with PLLA treatments. However, many lines that are in other areas will remain unaffected and require injections with other products or treatments with lasers.

Treatment of moderate to severe nasolabial creases can be effected with several products approved for the treatment of this area. Selection of the product used for this purpose depends on patients' skin type, skin thickness, tolerance for risk, goals, and budget. Evolence, Restylane, Perlane, Juvederm, Juvederm XC, and Radiesse are all products that will do well in this area. When injecting patients who have thin skin and moderate rhytids, it is wise to inject a clear hyaluron gel for the first injections. This is even truer when the product will be placed closer to the epidermis to etch out lines. Thicker, opaque products, such as Evolence and Radiesse, offer the potential to have longer-term corrections with a single injection session, but have adverse events that are potentially more long lived and more difficult to manage than the hyalurons. Thus, they are more appropriate for advanced injectors or for patients that have been treated previously. When combined with PLLA injections of the cheeks, average patients will require approximately 2 mL of filler in the nasolabial creases.

Perioral rhytids are a frequent companion of malar volume loss. Treatment of these lines with PLLA is inappropriate as it will lead to a high rate of

subcutaneous papules. However, treating these lines with botulinum toxins, lasers, and fillers may produce dramatic results. For the majority of patients who have moderate to severe perioral rhytids, injections with hyaluronic acid will produce significant improvements. Products well suited for this indication include Prevelle, which is also short lived and useful as a test product for this indication, Juvederm, and Restylane. The addition of 1 to 2 units of Botox or 2.5 to 5 units of Reloxin for hypertrophic orbicularis muscles may help to improve these lines.¹⁰ For some patients, even after fillers are used, it is useful to have the surface of the skin polished with either a fractional ablative or fractional nonablative laser. Since the perioral area is a center of attention, it is reasonable to use combinations of treatments to address it and to treat this area in conjunction with treatments of other areas.

Fillers are also helpful in treating superficial marionette lines. Thus, it is possible to restore volume in the prejowl sulcus while having residual lines in the superficial and mid dermis. Restoring this layer of correction with a volume filler is a rational complement to PLLA injections. Several products may be used to treat marionette lines with common ones including Juvederm, Restylane, Perlane, Evolence, and Radiesse. When injecting this area, one needs to be aware of the potential for product migration into the vermilion of the lip.¹¹

FILLERS WITH FILLERS

The advent of so many fillers to the United States markets has brought possibilities for combinations that can achieve results that were not attainable with the limited selection available a few years ago. Intuitively, thick fillers that are structural may be used for deeper creases, whereas thinner products may be used to treat superficial lines closer to the epidermis. Fillers with anesthetic may be used to make areas more comfortable before injection of products without anesthetic.

The most obvious method of combining different fillers is either geographically or spatially, that is, using different products in different locations or different products at different times. Thus, patients that have had a positive outcome from a short-lived HA may get a longer-term product injected at a subsequent visit. The initial HA will most likely still be extant and the combination will likely produce some synergy. Geographic combinations are another common injection strategy. Largely based on anecdotal evidence and personal experience, some fillers in the same category have become preferred for certain

426 locations. Patients presenting for treatment of
427 several facial issues may get Juvederm Ultra in
428 the tear trough and UltraPlus in the lips, while
429 getting Restylane in the nasolabial crease, and
430 Perlane in the marionette lines.

431 In addition to temporal and geographic separa-
432 tion, products may be layered on each other or
433 mixed together. Thus, structural fillers that are
434 useful for deep-tissue filling or support include
435 CAHA, Perlane, and to some extent, Evolence.
436 Each of these may be used and has the ability to
437 provide significant lifting. However, properties of
438 each limit their utility for filling lines.

439 CAHA provides a matrix that provides initial
440 correction with subsequent collagen and elastic
441 tissue ingrowth that helps to support the overlying
442 structures. However, it is an opaque, white
443 product that can be visualized when placed too
444 close to the epidermis. In addition, when injected
445 in the superficial dermis, it may produce nodules.
446 Although it is suitable for deep-tissue placement,
447 it is not appropriate for superficial line filling.
448 However, combinations of this product with other
449 fillers can address both facets of the aging face.
450 Products that may be layered above CAHA include
451 Restylane, Juvederm, and Prevelle. Each of these
452 may be injected superficially with a 30-gauge nee-
453 dle to lift the wrinkle away from the underlying
454 CAHA and to fill the superficial lines. Which of
455 these is selected depends on a variety of factors
456 including the thickness of the skin and the physi-
457 cian's experiences. Each may be injected with
458 a linear threading, serial puncture, or a combina-
459 tion of techniques.

460 Combinations of hyaluronic acids can also be
461 used to optimize patients' results. For instance,
462 different hyalurons may be used to treat different
463 parts of the anatomy or they may be layered
464 upon each other. Injections into the tear troughs
465 and lips require different properties than structural
466 lifting of the zygoma. For the tear trough and lips,
467 patients who have thin skin may benefit from injec-
468 tions with Juvederm. However, these patients may
469 require more Perlane for their marionette lines or
470 Restylane for their nasolabial creases. Additional
471 combinations include the intermarriage of Perlane
472 injections into the deep layer for volume, or
473 contour correction with Juvederm, or Restylane
474 injected superficially to smooth the superficial
475 layers. Temporal combinations may also benefit
476 certain patients. For instance, some patients that
477 are injected with one filler may return for an
478 enhancement procedure. These enhancements
479 are typically performed with the same product
480 that was originally injected. However, there are
481 instances where a thicker, more structural hyaluron
482 must be injected deep to the prior injection to

483 change the contour, and other circumstances
484 where a softer product may be layered superfi-
485 cially to the structural product to etch out a line
486 that is the focus of the patients' attention. Although
487 the literature demonstrates that enhancement
488 injections with the same product results in
489 a more durable correction (through mechanisms
490 not yet defined), there is no reason to believe
491 that this same phenomenon will not occur when
492 different hyalurons are injected together.¹²

493 The areas that are commonly treated with these
494 combinations are the nasolabial creases and the
495 marionette lines. On average, a woman with
496 moderate tissue loss of the nasolabial creases
497 will require between 1 to 1.3 mL of Radiesse per
498 nasolabial crease with about 0.5 mL of hyaluronic
499 acid layered superficial to it. Marionette lines may
500 be treated with less volume and many women can
501 be effectively treated with 0.65 mL of Radiesse
502 and about 0.5 mL of hyaluronic acid superficial
503 to this. As with injections of single products, it is
504 essential to inject the angles of the mouth with
505 some hyaluronic acid to restore a horizontal
506 projection to this area.

507 Evolence is an opaque, cross-linked porcine
508 collagen that can also provide long lasting (up to
509 9–12 months) support for the marionette lines
510 and nasolabial creases. Many nasolabial creases
511 are adequately treated with 1 mL of Evolence on
512 each side. Treatment of the marionette lines is
513 also easily accomplished with Evolence. Average
514 volumes for this treatment should begin with 0.5
515 mL on each side. However, as with Radiesse,
516 one cannot place Evolence too close to the
517 epidermis for risk of creating visible papules.
518 Thus, it is helpful to layer a hyaluronic acid superfi-
519 cial to the Evolence when treating lines that have
520 a superficial component in addition to the deeper
521 loss of volume.

522 Silicone is a permanent soft-tissue augmenta-
523 tion product that is used in an off-label manner.
524 It has been combined with various additives over
525 the years, frequently with disastrous results.¹³ Sili-
526 cone has been inadvertently combined with
527 numerous products as patients who had been
528 treated with this agent in the past present for injec-
529 tions of additional products. Among the frequent
530 combinations that occur are silicone with collagen
531 and silicone with hyaluronic acid. Because silicone
532 can cause granulomas, even after being dormant
533 for many years, there is some potential for prob-
534 lems in areas that contain silicone. In addition, sili-
535 cone may be encapsulated and present a flow
536 barrier to soft-tissue augmentation products,
537 such as hyaluronic acid. Thus, it is recommended
538 that combinations of other soft-tissue augmenta-
539 tion products with silicone proceed gradually and

that the risks and benefits be presented to patients before treatment. In some instances, fillers may be combined with silicone to mask a contour deformity created by this product.

SUMMARY

Soft-tissue augmentation has evolved enormously in the past few years and we are just learning optimal methods of using and combining products already on the market. Clearly, some of the products introduced have not been commercially accepted for reasons of safety, efficacy, or market demand and it is likely that many more products of dubious distinction will also be introduced. However, the vast majority of products used for soft-tissue augmentation will find niches in which they excel.

Whether we are using different types of HA, HA with collagen, PLLA with HA, or any of the other myriad of combinations available, we now have the ability to address the root causes of facial aging in a manner not even conceivable a few years ago. Truly, this is an interesting and exciting time to be in this specialty.

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