Soft Tissue Augmentation with ArteFill

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ABSTRACT

ArteFill is a novel, third-generation polymethylmethacrylate (PMMA) injectable filler with unique properties. When compared with predecessor materials, ArteFill demonstrates improved biocompatibility as a result of more uniform PMMA microsphere size and shape. This translates into less adverse events after placement. ArteFill can provide a permanent volume enhancement by stimulation of fibroblasts that encapsulate nonabsorbable microspheres with collagen deposition. Currently, ArteFill is FDA approved for permanent augmentation of moderately deep nasolabial folds. It is also commonly used off-label for augmentation of other skin creases and regional areas of volume deficiency, such as the tear trough–malar and marionette line–prejowl sulcus regions. The key to success with ArteFill is a conservative approach with avoidance of overcorrection. Proper technique includes deep dermal to subcutaneous placement with full correction achieved gradually over several treatments. Complications are mostly limited to nodule formation, which is easily managed in most cases with conservative intervention.

KEYWORDS: ArteFill, polymethylmethacrylate (PMMA) microsphere, permanent injectable filler

One of the earliest signs of aging is a loss of facial fullness and the development of wrinkles. Softening of these facial lines and the restoration of volume and fullness in the face often can be achieved nonsurgically with injectable fillers. Injectable fillers have evolved to become one of the most popular choices for noninvasive facial enhancement. These include a wide variety of fillers with increasing numbers having been introduced over the past several years. Unfortunately, nearly all of these fillers reabsorb generally within 12 months, necessitating repeat treatment. In an effort to overcome this limitation, a group of nonresorbable filler products composed of polymethylmethacrylate (PMMA) microspheres were introduced in the 1990s. Such fillers provide a durable aesthetic enhancement after placement unmatched by absorbable products. Since that time, several generations of PMMA filler have been developed with the latest and most novel being ArteFill (Artes Medical Inc., San Diego, CA).

PERMANENCY OF ARTEFILL

Most materials used as biological fillers to increase the thickness of the dermis or underlying subcutaneous tissue begin to dissolve within a few months. If one is seeking to achieve permanent soft tissue enhancement, they must use either an autogenous material that becomes vascularized and survives as a graft, such as fat, or a nonresorbable synthetic substance, such as ArteFill. When ArteFill is injected beneath the skin surface, the nondegradable microspheres serve to stimulate fibroblast activity. Contained within each cubic centimeter (cm^3) of ArteFill is approximately 6 million PMMA microspheres, individually stimulating such activity. ArteFill

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also contains bovine collagen that is used as a carrier substance to prevent clumping during injection. As the bovine collagen is absorbed, it is replaced by the patient's own collagen, which begins to permanently encapsulate the PMMA microspheres. By volume, this matrix is composed of ~20% PMMA microspheres and 80% autologous connective tissue deposition.[1] The end result is a layer of biologically stabilized PMMA that resists migration and resorption while providing enduring soft tissue volume enhancement.

BIOCOMPATIBILITY OF ARTEFILL

ArteFill is considered a third-generation PMMA filler following the introduction of Artecoll, the second-generation product, and ArtePlast,[Q1] the first-generation formula. Like its predecessors, ArteFill is composed of PMMA microspheres suspended in a collagen gel matrix. There are, however, unique distinctions between ArteFill and its predecessors in terms of biocompatibility.

The biocompatibility of PMMA has been well accepted since Judet[2] introduced the first hip prosthesis made from PMMA in 1947. Since that time, however, we have learned a great deal more about the biocompatibility of PMMA when used as an injectable filler. One of the main criticisms of Artecoll and ArtePlast involved an unacceptably high rate of granuloma formation after injection in the skin. This included both early and late manifestations.[3] It was discovered by use of scanning electron microscopy that these adverse events were largely related to biocompatibility issues with microsphere size and shape in the early-generation products. For instance, these products contained a high percentage of microspheres less than 20 μm in diameter. Particles of this size and smaller were thought to promote phagocytosis and, thus, increase the frequency of adverse events. In addition, microspheres in these earlier products possessed a more irregular particle surface contour that made them more prone to causing granulomatous reactions.[4–6]

Based on this early clinical experience with Artecoll and ArtePlast, substantial improvements were made in the manufacturing process resulting in the product we now know as ArteFill. These refinements included increasing the uniformity and consistency in microsphere size, which at 30 to 50 μm in diameter minimizes the incidence of phagocytosis. The proportion of particles that are less than 20 μm in diameter has now been reduced to <1%, and, in fact, are typically nondetectable in the finished product. The surface contour of ArteFill microspheres was also greatly improved to generate smoother, rounder particles that further resist phagocytosis. Furthermore, ArteFill is now manufactured in the United States using bovine collagen sourced from a restricted, closed herd. Collectively, these fundamental changes in the product were instrumental in ArteFill becoming the only U.S. Food and Drug Administration (FDA)-approved permanent injectable filler available for use in augmentation of the nasolabial folds.[7,8]

CLINICAL INDICATIONS

Like nearly all temporary injectable fillers, the indications for ArteFill use has steadily increased over the past several years. One of the most popular indications is smoothing out unwanted facial creases and wrinkles. As a result of the aging process, the collagen framework that normally provides dermal support gradually begins to loosen. Over time, this results in thinning and focal reduction of soft tissue volume. Eventually, this leads to formation of a skin crease or wrinkle. With further aging, these changes can deepen into what are essentially skin folds. When ArteFill is used to treat such creases and wrinkles, the goal is to replenish lost dermal collagen while volumetrically expanding the dermal layer. Thus, the term *dermal filler* commonly used to describe this particular application. Given its permanent nature and potential for nodularity, ArteFill is best suited for placement in the deep dermis for treatment of moderate to severe skin creases and wrinkles. Therefore, one should refrain from choosing this filler for correction of finer wrinkles that necessitate placement closer to the superficial skin surface. It is also relatively contraindicated for mucosal lip augmentation for similar reasons.

Treatment of a deepened nasolabial fold is perhaps the popular indication for ArteFill use. In fact, it should be pointed out that currently, the only FDA-approved indication for use of ArteFill in the United States is augmentation of the nasolabial fold. Use of ArteFill in any other capacity is considered an off-label indication and should be discussed as such with potential patients. When discussing ArteFill use for the nasolabial fold, patients should be made aware that it is aesthetically acceptable to have a fine line between the cheek and upper lip. It is typically when this line deepens and creates an abnormal shadow that ArteFill may be indicated. The goal of treatment should be to restore a fine or shallow line rather than totally erase any perception of demarcation. In patients who have undergone prior facelift surgery, ArteFill augmentation of the nasolabial fold can be a powerful complement to further enhance their results.

Another widely popular indication for ArteFill use is regional volume deficiency in the face. This refers to broad aesthetic subunits, or regions, of the face that are lacking in sufficient shape and contour. Common examples of this include the tear trough–malar and perioral (including the marionette lines and prejowl sulcus) regions. Unlike creases or wrinkles, these abnormalities typically result from volume deficiency below the dermal plane. In many cases, this involves patients seeking to enhance a certain area that is naturally

deficient in volume. In others, ArteFill is being used to rejuvenate or correct deficiencies more related to aging or iatrogenic causes.

A recent and growing indication for ArteFill use is an unsatisfactory nasal appearance. In patients who would otherwise undergo augmentation rhinoplasty, ArteFill can be used to elevate or project certain areas of the nose, such as the radix and bridge. This is often referred to as *injection rhinoplasty*. ArteFill has also been used successfully in revision rhinoplasty patients who note persistent postoperative contour irregularities or depressions. Instead of undergoing a complex and potentially risky secondary rhinoplasty procedure, ArteFill has been used as a minimally invasive alternative to achieve the anticipated result. It should be emphasized that such use of ArteFill should be reserved only for patients with a relatively thick soft tissue envelope who can tolerate placement of a permanent filler.

PATIENT EVALUATION AND PREPARATION

Successful use of ArteFill begins with a conservative overall approach, perhaps more so than any other injectable filler. In essence, this translates into avoiding overcorrection. After all, the changes noted can be permanent. In some cases, it may be prudent to recommend a temporary filler prior to ArteFill use so that patients are more comfortable with the potential changes that will be visible. All patients undergoing injection of ArteFill absolutely must be apprised of the potential for late problems because of the permanent nature of the filler. This is an aesthetic procedure, and it is mandatory to educate patients of all potential adverse events during the informed consent process.

In the past, injectable fillers have unfortunately been mischaracterized as single-session enhancement procedures. When using ArteFill, however, all patients should be prepared that this involves a staged process that extends beyond the first treatment session. Patients should be counseled the first treatment is intended to achieve a visible improvement. For optimal results, however, a follow-up appointment is necessary 4 to 6 weeks later for further augmentation and refinement.

Preparation also includes a detailed discussion to establish realistic expectations for the planned treatment area. Obtaining a medical history will help ensure absence of a known propensity for hypersensitivity or allergic response. Because of the presence of bovine collagen, ArteFill requires that all patients undergo appropriate skin testing several weeks in advance of their planned procedure. Other contraindications, such as pregnancy, lactation, and a history of keloid or hypertrophic scar formation, should also be ruled out.

Aesthetic analysis and determination of the volume-deficient areas is accomplished with a thorough physical examination. This should also include notation of any preexisting asymmetries, contour irregularities, and skin blemishes that may alter the proposed treatment outcome. Photodocumentation using adequate lighting and standard views is recommended to more accurately assess treatment outcomes.

Beginning 10 to 14 days prior to ArteFill injection, patients are asked to refrain from taking any medication that would potentially act as an anticoagulant. Failure to do so increases the likelihood of unwanted bruising and swelling. Whenever possible, the patient is also advised to begin taking *Arnica montana* 2 days prior to and 5 days after treatment to further help minimize bruising.

INJECTION TECHNIQUE

Prior to injection of ArteFill, it is important to allow the syringe to thaw for 30 to 45 minutes. The product requires refrigerated storage and is quite dense until it is allowed to warm to room temperature. If injection is attempted too soon, there is significant resistance in the syringe making accurate placement of the filler quite challenging. Once adequately thawed, however, the material flows very easily and is comparable with most temporary injectable fillers in terms of handling characteristics.

Patient comfort with ArteFill injection is paramount to avoid excess bruising and swelling. Fortunately, ArteFill is manufactured with 0.3% lidocaine contained within the filler, which helps with patient comfort during deposition of the filler. Despite this, other anesthetic measures should be taken to minimize pain related to initial needle entry. The simplest measure involves use of a cold compress applied immediately prior to and after treatment. Another popular method is application of a topical anesthetic to the skin 45 to 60 minutes prior to treatment. This should be done only after thoroughly cleansing the skin surface of all makeup and oil. For perioral injections, a cotton tip applicator can be used to swab the upper and lower labial sulcus minutes prior to filler placement. In cases where topical methods are thought to be insufficient, local or regional nerve blocks can be used. When using such blocks, careful attention must be paid to avoid excess infiltration as this may distort soft tissue contour and decrease accuracy of filler placement.

ArteFill is injected through a 26-gauge, -inch needle packaged with the syringe or a standard 27-gauge needle. Using the nondominant hand, the surrounding soft tissue is stretched to stabilize the skin surface for needle insertion. After insertion, the bevel should be positioned downward to minimize unwanted deposition of the filler in a more superficial plane.

CLINICAL APPLICATIONS

Nasolabial Fold Augmentation

Injection of ArteFill into the nasolabial fold is generally straightforward. The needle is typically inserted at the inferior border of the fold and advanced superiorly toward the alar-facial junction. It is important to be in the proper depth, which is the deep dermis. When injecting into the correct deep dermal plane, the needle should slightly tent the overlying skin. When properly placed, one should see immediate plumping of the skin and noticeable improvement as the needle is withdrawn. If the silver of the needle is visible through the skin, do not inject as a ridge or nodule could easily develop. When the needle is placed too deep, the material is largely deposited in the subcutaneous layer and provides little actual augmentation of the fold. In addition, this can lead to a cord of filler material that is easily palpable along the underlying mucosal surface.

Ideally, injection is performed using a linear threading technique (also known as tunneling) as the needle is withdrawn. Typically, two to three linear strands of ArteFill are placed medial to the fold to properly efface the crease. In many patients, the superior aspect of the fold requires a layered injection because of more volume deficiency in this area. Approximately 1 to 2 syringes (0.8 cm^3 each) of ArteFill are usually necessary to achieve a clinically significant bilateral improvement. Injection should be stopped prior to the needle being removed from the skin to avoid superficial placement of filler at the needle entry site. If this does occur, the unwanted material can generally be easily expressed through the entry site using a gloved fingernail. A second injection session is often necessary to achieve full correction of the nasolabial folds, especially along the inferior aspect of the crease.

Tear Trough–Malar Augmentation

Management of the tear trough is usually done with linear threading or serial puncture technique. With careful technique, ArteFill can be used effectively to augment the underlying soft tissue and smoothly transition the lower eyelid and cheek (Fig. 1). In patients with thin skin, however, it is more prudent to choose a temporary filler for this purpose.

It is helpful to keep the patient in an upright position during injection of this region. When placed supine, periorbital fat tends to retract back under the eye, making accurate appreciation of the ongoing correction process somewhat difficult. The needle is inserted from lateral to medial just inferior to the deepest aspect of the tear trough. Careful attention should be paid to maintain a 2- to 4-mm distance from the lateral nasal wall as filler placement in this area can inadvertently widen the appearance of the nose. Care should also be taken to avoid injection above the level of the orbital rim to minimize risk of injection behind the orbital septum and possible damage to the eye. The intended plane of injection is supraperiosteal, which maximizes native soft tissue cushioning of the ArteFill. On average, 0.5 to 1 cm^3 of filler is placed along each side, depending on the degree of rejuvenation desired.

Augmentation of the adjacent malar region is commonly done in combination with the tear trough. Radial fanning is the preferred technique in this area because of the broader region being injected. The entry site for the needle is several millimeters lateral and superior to the bony malar eminence. Radial tunnels are then used to deposit the filler along a supraperiosteal plane. As the injections transition laterally and inferiorly away from the thin skin of the lower eyelid, placement can be safely shifted to a more subcutaneous tissue plane. In general, 1 to 2 cm^3 are usually sufficient for each side to create more convexity along the malar region.

Perioral Augmentation: Marionette Lines–Prejowl Sulcus Region

ArteFill injection of the perioral region may be more challenging than that for other areas because of the relatively thinner soft tissue layers. With careful and proper technique, however, excellent results can be achieved. The injection plane is combined deep dermal and subcutaneous. In many patients, there is not only a deep line extending from the oral commissure but also loss of volume in the surrounding area. Treatment should begin along the lower white roll of the lip with injection horizontally about 1 cm in length from the corner of the mouth. Care should be taken to avoid injection into the mucosal lip and deep into the orbicularis oris muscle as this can lead to unwanted palpability. Next, 5 to 10 vertical and/or horizontal threads of ArteFill are placed using a cross-hatching or radial fanning technique. If necessary, extension toward the mandibular border can be done to help augment the prejowl sulcus as well. In some cases, injection goes just below the mandibular border if more jowling is present. This injection can extend from the anterior margin of the jowl toward the midline of the chin to help restore a more youthful transition between these points. Distribution of the filler often ends up following the shape of an inverted triangle with the lateral margin based on the deepest marionette line. Between the marionette lines and prejowl sulcus, a total volume of 2 to 3 cm^3 of ArteFill is usually sufficient to achieve adequate correction. Preferably, this is done over two or more sessions to achieve ideal results with minimal complications.

Nasal Reshaping

Use of ArteFill for nasal reshaping is best done with meticulous serial deposition technique. When

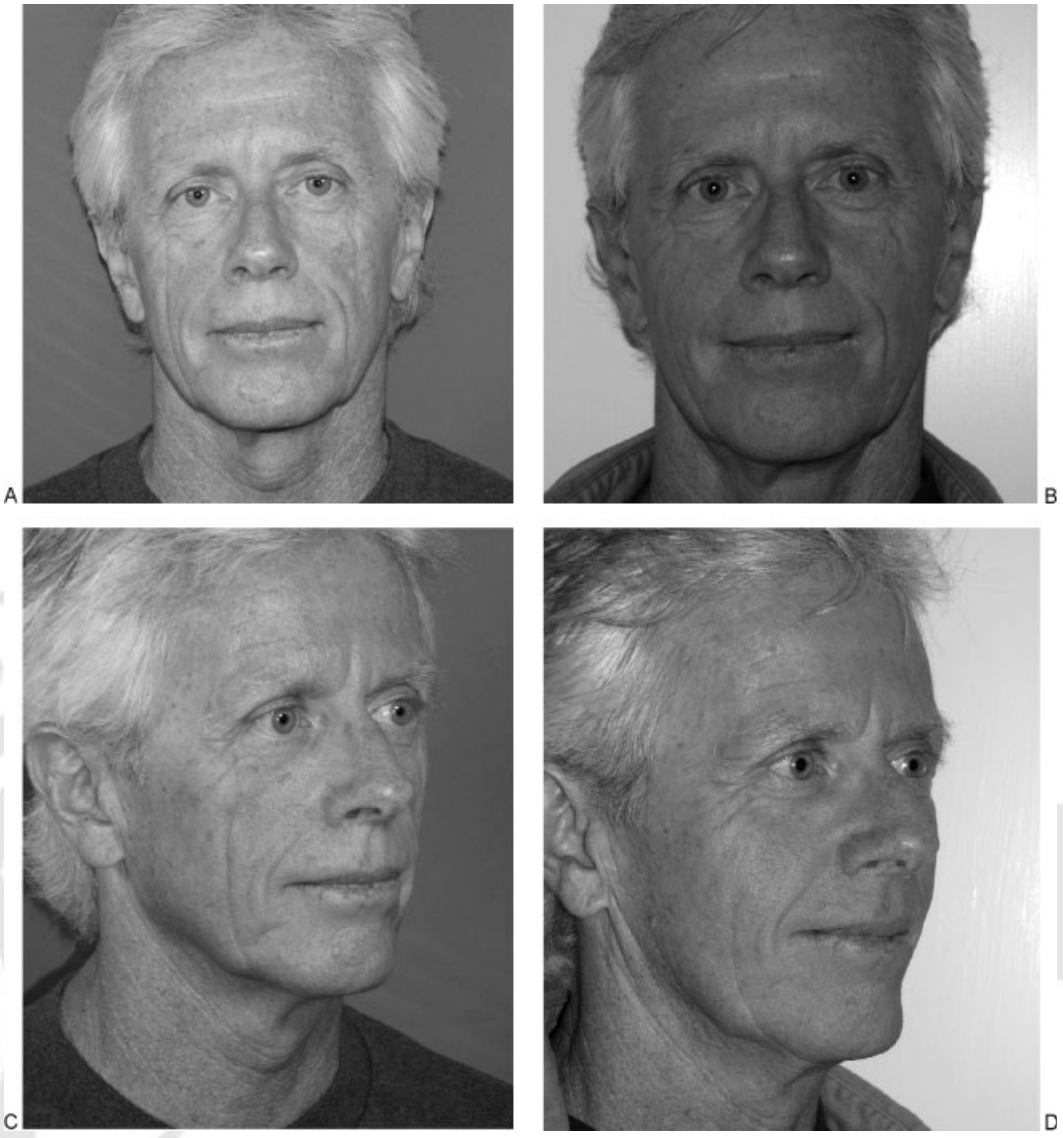

Figure 1 Example of ArteFill injection to augment the cheek region in this middle-aged male patient. This patient was bothered by loss of soft tissue volume in the midface region, contributing to an undesirable hollowed and tired appearance. He underwent injection of nearly 2.4 cm^3 ArteFill over several sessions to enhance both sides of the face. Notice overall improvement in the deep skin creases with a more convex cheek to lower eyelid contour after treatment. (A) Frontal before; (B) frontal after; (C) oblique before; (D) oblique after.

augmenting the nose, whether it is the tip, supratip, or bridge, millimeters of change can make a noticeable difference. Therefore, serial microdeposits are recommended to gradually attain the desired shape. Using this technique, multiple deposits can be safely positioned adjacently below the dermis and immediately above the nasal skeleton. It is often beneficial to use the nondominant hand to pinch the bridge or tip during the actual injection. This minimizes chances of diffusion of the filler along the sides that may contribute to the appearance of an undesirably wide nose. Digital massage of the treated area then often helps to blend the filler, particularly when augmenting a depression along the bridge. It is unlikely that more than one syringe of ArteFill would be used in this capacity, with most patients requiring less than half of a syringe on average.

AFTER-TREATMENT CARE

A cold compress is helpful during the first 72 hours after treatment to minimize swelling and ecchymosis. Care must be taken, however, to avoid undue pressure that would potentially cause unwanted displacement of the filler. Patients are asked to limit facial animation for several days after injection as this can sometimes cause unwanted displacement of the filler. Patients are asked to return 2 to 4 weeks later for interval examination and repeat injection as necessary.

COMPLICATIONS

A minor contour irregularity, or nodule, is the most commonly observed adverse event after ArteFill injection. In some cases, these are recognized immediately and can be easily massaged down by the injector. Other contour irregularities may manifest days to weeks later. Most involve an erythematous swelling representing clustering of the PMMA microspheres in a small focus. Steroid injections may be helpful if the nodule is caused by scar encapsulation. Only a small amount is injected to avoid skin atrophy. The needle can also be used simultaneously to mechanically break down the nodule and any evolving scar tissue. The patient is also asked to vigorously massage several times a day for 3 weeks. In some circumstances, it is necessary to remove the filler material. This is generally a simple matter that is accomplished through a small intraoral incision using finger palpation. A fine hemostat can be inserted and the material gently grasped with removal until the irregular contour disappears.

Other erythematous irregularities represent true granuloma formation. True granulomas involve infiltration of collagen fibers in between PMMA microspheres, which are pushed apart, with rare lymphocytes, macrophages, and giant cells noted.[9] If a true granuloma forms, it would be expected to occur at all injection sites simultaneously. The authors have experienced no cases of true granuloma formation, but should this occur, intralesional steroids, potentially a short course of oral steroids, and, in some cases, intralesional 5-fluorouracil may be needed. It is helpful if a biopsy can be obtained and a true granulomatous reaction confirmed histologically.

CONCLUSION

ArteFill is a novel, third-generation PMMA-based injectable filler with unique properties when compared with predecessor materials. Its favorable biocompatibility profile is derived from more uniform PMMA microsphere size and shape, contributing to less adverse events after placement. ArteFill provides patients with permanent soft tissue enhancement by stimulating a fibroblastic deposition of collagen around the nonabsorbable microspheres. The end result is a biologically stable matrix that creates a durable, long-lasting cosmetic enhancement. Currently, ArteFill is the only FDA-approved permanent soft tissue filler for use in augmenting moderately deep nasolabial folds. It is also commonly used off-label for augmentation of other facial skin creases and regions of volume deficiency. An essential key to successful use of ArteFill is a conservative approach with avoidance of overcorrection. Proper technique includes deep dermal to subcutaneous placement with full correction achieved gradually over two to three treatment sessions. Complications are fortunately limited mostly to nodule formation, which is generally easily managed.

DISCLOSURE

In December 2008, Artes Medical Inc., the manufacturer of ArteFill, filed for bankruptcy.

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