
Polymethylmethacrylate Microspheres/Collagen as a Tissue Augmenting Agent: Personal Experience over 5 Years

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BACKGROUND. Polymethylmethacrylate microspheres/collagen has been used in Canada since 1998. A closely related product will probably be approved in the United States shortly. Concerns have been expressed about the use of permanent fillers such as this.

OBJECTIVE. This retrospective study of the authors' clinical practice is designed to reflect their experience with this agent. In particular, the authors describe some of the problems they have seen.

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ARTECOLL IS an injectable augmenting agent that uses a patented microsphere technology. It consists of microspheres of polymerized methylmethacrylate (PMMA) in a bovine collagen vehicle. This product was developed by a German plastic surgeon, Gottfried Lemperle, and has been used in Europe since approximately 1993 under the name Artecoll. Prior to that time, a similar product, Arteplast, contained many smaller and less smooth particle sizes and had a significant tendency to induce long-term granulomas.¹ The switch to Artecoll has caused some confusion between the granuloma-forming potential of the two products.² Artecoll has been in use in Canada since 1998 and has been well received by consumers and physicians alike. However, reports of long-term complications appearing long after injection have caused concern among injectors about its long-term safety. This article describes our clinical experience with the use of Artecoll in approximately 500 individuals and some of its complications. It attempts to assess the potential of this material.

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RESULTS. Polymethylmethacrylate microspheres/collagen has behaved as a satisfactory long-term tissue augmenting agent in the authors' practice. They have had the opportunity of managing any number of patients with Artecoll granulomas and describe these patients.

CONCLUSION. When polymethylmethacrylate microspheres/collagen is introduced to the United States, practitioners will need to learn how to use this exacting agent and will obtain excellent results with careful use.

Patented Microspheres

Artecoll is in the late stages of the US Food and Drug Administration's (FDA) approval process and is expected to receive approval for wrinkles and soft tissue contour deficiencies (such as acne and traumatic scars) under the name Artefill (Artes Medical, San Diego, CA, USA). Artecoll is a suspension of 20% polymethylmethacrylate (PMMA) microspheres of 30 to 42 μm diameter in an 80% bovine collagen solution as a delivery vehicle.¹ After injection, the collagen solution is slowly absorbed, leaving behind the nonbiodegradable PMMA microspheres. Given that PMMA is not broken down in the body, the microspheres in Artecoll are permanent, although its manufacturer is careful to describe the correction only as "long term" because the aging process will continue, and the longest clinical experience to date is 10 years.

As the collagen disappears, the correction is reduced, but fibroplasia appears to partially reverse this loss after 1 or 2 months, although the final result is not present for approximately 6 months. The collagen used in Artecoll is partially denatured, so it is less likely to cause an allergic reaction than, for example, Zyderm (INAMED Aesthetics, Santa Barbara, CA, USA), and we have seen less frequent reactions to the Artecoll test injection than to Zyderm. It is approved for use without a skin test in some European

countries and in Canada, but we always do a single intradermal collagen skin test prior to use and have not seen collagen-type allergy in skin test–negative individuals. The only two individuals whom we have seen produce a positive skin test to the collagen in Artecoll were also skin test positive to Zyderm. Because of the remote possibility of transfer of prion disease, the source of the collagen has been changed from European- to US-derived hides.

Clinical Technique

Artecoll is used as a deep dermal or superficial subdermal augmenting agent. The main areas of use are for the correction of depressed scars, such as acne scars, and to replace lost facial fat owing to the aging process. The nasolabial folds, melomental folds, mental crease, and nasojugal folds are all regularly treated. In addition, Artecoll can be used to fill in hollowed cheeks, to augment the zygomatic prominence and the mentum, and generally to sculpt the face in a way that was not possible with injectable collagen.

Having determined an appropriate indication in a non–bovine collagen–sensitive individual, injection of Artecoll is highly technique dependent. The syringe contains 0.5 mL of the product in a 1 mL syringe with a Luer-Lok. A 26-gauge needle is provided, and this is much more satisfactory than the former 27-gauge needle. The RJ Maxflo 30-gauge needle, which has an internal diameter similar to that of a 27-gauge needle, is much more comfortable for the injectee but will block occasionally. Pain relief can be improved with ice or topical local anesthetics, such as LMX (Ferndale Laboratories Inc., Ferndale, MI, USA) or Betacaine (Hunter's Pharmacy, Windsor, ON, Canada). Occasionally, we use nerve block anesthesia in the perioral area.

In planning Artecoll injection, it is important not to aim for complete correction in a single treatment session. In most clinical situations, two to four sessions will be necessary before the final result is achieved, and the treated individual must be aware of this. In situations such as correction of the nasolabial fold, many subjects will wish for more correction than can safely be achieved in the first Artecoll treatment session, and we often overlay the Artecoll with Restylane or Perlane in that situation; as the hyaluronan slowly dissipates, further Artecoll injections will maintain the correction.

The actual injection technique for Artecoll is unique. Originally, we tried to emulate the microdroplet technique, which was used for injectable silicone. However, Artecoll is not easily injected in tiny amounts. It is much better to inject "microstrands" by keeping the needle tip moving continuously and at the same time gently pressing on the plunger of the syringe. The material should flow smoothly into the tissues. If greater pressure is required, then something is wrong, the injection should be stopped, and the needle should be

withdrawn from the skin. Flow of the Artecoll should be checked because the most likely cause of greater pressure being needed is a blocked needle. The other cause is when injection is being attempted into scar tissue. Because of the variability of flow in this situation and the probability that Artecoll will be deposited irregularly or in clumps, injection into sclerotic tissue should be attempted very cautiously.

Lips

When the FDA panel met in February 2003, it recommended that injection into lips be a contraindication because of the reports of lumpiness in lips. However, injection into lips is commonly performed in Canada and is certainly possible, with some precautions. First, it is essential not to inject too much material into the lips (or indeed elsewhere!). It is our rule never to inject more than one syringe per lip in one session, and we often inject considerably less. We generally deposit a line of the material approximately 3 mm on to the vermilion of the lip. We find that injecting more deeply into the lip, such as in the front of the teeth, tends to form lumps that are obvious to the individual. Layering a temporary filler, such as a hyaluronan, is quite acceptable. In addition, we inject into lips only on a maximum of two occasions, probably because we prefer to be conservative and do not wish to cause lip lumps or excessive augmentation. Again, further correction must be performed with temporary fillers only. Finally, it is ideal to relax the orbicularis oris with botulinum toxin prior to Artecoll injection so that the normal pursing action of that muscle is less likely to cause the material to aggregate into bumps.

Even with this careful technique, it is possible to detect some lumpiness, and it is important to warn the subject prior to lip injection that minor lumpiness is the rule rather than the exception. Occasionally, more significant lumps will develop. Sometimes these will resolve over a period of 6 months. Occasionally, they need treatment, and it is a simple matter to make a small incision in the mucosal surface of the lip under anesthesia and to gently remove the offending material. If this is sent for histopathologic examination, it will be reported as a foreign body granuloma. It is very important to distinguish this clinical situation from the true Artecoll granuloma (AG), which is a much more obvious and serious adverse event. It is our belief that these lumps in lips simply represent poor technique and the limitations of the product rather than an immunologic reaction. Rather, correction with Artecoll should occur over two to four treatment sessions, with conservative amounts and long intervals between injections recommended.³ Many reactions are directly related to poor injection techniques or technical mistakes, including uneven distribution, superficial implantation, or implantation in the wrong location (ie, into facial muscles), with too much volume. Incorrect technique can lead to long-lasting red-

ness, visible irregularities, inadequate wrinkle improvement, or palpable lumps or strands.

Artecoll Granulomas

Although Artefill has not yet been approved for use in the United States, it has been in use for 10 years in Europe and 5 years in Canada as Artecoll. This long-term use outside the United States has raised a number of questions about the safety of Artecoll. Even with a conservative approach, AGs have been reported to appear months—even years—after treatment.⁴

Because of this, Artecoll has garnered a great deal of negative publicity, some of it unfairly. A recently published report of a granulomatous reaction to Artecoll is a good example of misinformation that can occur: when contacted, the author confirmed that the material injected was actually Arteplast, the original precursor suspension of irregular PMMA microspheres with a known propensity to produce granulomas.^{1,2}

Artecoll may produce granulomas in a small number of those injected; however, the incidence of true granuloma formation—histologically distinguished from simple nodules and bumps by the amount of epithelioid cells, histiocytes or macrophages, lymphocytes, inflammatory cells and eosinophils, polymorphous exudates, and multinucleated giant cells⁵—is likely very low and has been described as a rare event, occurring in less than 0.01% of patients.¹ In the US clinical trials under evaluation for FDA approval, no AGs were reported in 251 patients across eight centers, with follow-up now for 5 years.

A typical case of AG was described by Alcalay and colleagues.⁶ Their case report described a 54-year-old woman presenting with longitudinal hard nodules and overlying erythema in the glabella and nasolabial folds 15 months following a total of 1.5 cc Artecoll injections.⁶ Two years after the injections, microscopic examination provided histologic diagnosis of true granulomas. Whereas the nodules in the glabella resolved completely with triamcinolone (Kenalog) injections, those in the nasolabial area reappeared lower in position after applying pressure.

More recently, Kim and colleagues reported the case of a 56-year-old Korean woman who presented 4 years after Artecoll injection with multiple, well-demarcated, linear, skin-colored to brownish, firm plaques on the anterior neck along the wrinkle lines.⁷ Microscopic examination revealed the characteristics of foreign body granuloma resulting from Artecoll injection. The lesions responded to three injections of triamcinolone acetate. The authors suggested that Artecoll not be used as implant material in thin and constantly moving skin, such as that of the neck.

We have seen three individuals with AG in the past few months. All were injected with Artecoll by other physicians. The first is a 27-year-old female who had three syringes of Artecoll injected into the upper lip alone, one

syringe per treatment session on three occasions separated by some months. She had no problem until 2 years after injection, when the lip suddenly became enlarged and hard (Figure 1). She was treated with triamcinolone acetate 40 mg/mL,¹ approximately 0.5 mL on two occasions. She responded but then relapsed and was again treated on one occasion with triamcinolone. Subsequently, she was seen a year later with a normal-appearing lip and no clinical evidence of AG.

The second individual is a 46-year-old female who was treated with Artecoll on three occasions, the treated areas being the nasolabial folds, the mouth corners and melolabial folds, and the glabella. She had a satisfactory correction until 3 years postinjection, when all areas became hard, red, and tender (Figure 2). She has been injected with



Figure 1. Artecoll granuloma of the upper lip in a 27-year-old female appearing 2 years after treatment.



Figure 2. Artecoll granuloma in the nasolabial fold and mouth corner area seen in a 46-year-old female appearing 3 years after treatment.

up to 0.5 mL of triamcinolone acetonide 40 mg/mL on six occasions and is on allopurinol 200 mg daily. So far, her response is slow. She still has areas of firm induration, and she also shows some atrophy around these with prominent redness. She is now almost 2 years after the onset of AG, and her condition now seems to be resolving.

The third individual we have seen with AG is a 62-year-old female who had CO₂ laser resurfacing in the perioral area 4 years previously. Subsequent to that, she developed some scarring, which was treated by the operating surgeon with Artecoll on three separate occasions, one syringe per session. She had no problems until 1 month prior to our seeing her, when she had rapid onset of hard swelling with a red-blue color that was painful with pressure in all of the Artecoll-treated areas (Figure 3). Interestingly, when she was much younger, she was poked in the forehead with a pencil and had a small amount of residual graphite just under the skin. When the Artecoll areas became inflamed, so did this long-standing lesion! The histology of both the AG and the pencil lesion showed epithelioid histiocytes and multinucleated giant cells forming non-necrotizing granulomas. Intralesional triamcinolone therapy 40 mg/mL on four occasions at monthly intervals produced remission of the AG, and she had not been seen for approximately 1 year at the time of writing.

In addition to these three patients who were injected with Artecoll elsewhere, we have observed a 49-year-old female whom one of us injected in the glabella, nasolabial folds, mouth corners, and cheeks on three occasions over 6 months. Two months after the third treatment, she developed bruise-like discoloration and lumpiness in the cheek area only. This responded to injections of approximately 0.1 to 0.2 mL of triamcinolone acetonide 40 mg/mL injected on three occasions. Although the clin-

ical appearance in the cheek was very similar to that of the other individuals with AG described above, because of the early nature of this reaction and the fact that only one area was affected, we do not regard this as typical AG.

The opportunity to manage these cases of AG has had two effects on our practice. The first is the opportunity to see how these cases respond to treatment and if they will remain in remission once that is achieved. Second, we have become concerned about initiating Artecoll treatment in previously untreated individuals. At the present time (August 2005), we are now once again initiating Artecoll treatment because we believe that the product has been improved to reduce the risk of AG and that this condition can be satisfactorily managed in the majority of individuals affected. We are continuing to monitor the incidence of AG and the response to treatment of those individuals with AG who have come under our care.

Artecoll has been well established in Europe and Canada and with careful use appears to be safe, although the long-term safety of this and indeed any injected permanent filler is unknown. Many of the adverse reactions associated with Artecoll are likely due to poor technique and are no more than simple nodules rather than true granulomas, the formation of which is extremely uncommon, in our experience. As with all injectable fillers, choosing the appropriate sites and following proper injection guidelines and techniques will minimize the risk of any complications. The injecting physician must be aware of the "honeymoon" period after injection, and the patients should have this potential inflammatory sequel as part of their informed consent because it is important that the esthetic subject appreciate the differences between biodegradable and nonbiodegradable fillers before their treatment is given. Careful and accurate documentation of any complications is necessary to provide clinicians with an accurate perception of the safety and efficacy of Artecoll.

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Figure 3. Artecoll granulomatous scarring under the lower lip following CO₂ laser resurfacing. The granulomatous reaction began almost 4 years post-treatment.

Commentary

In September 2003, experienced Canadian Artecoll injectors in the Toronto and Montreal areas participated in round table discussions with Dr. Gottfried Lemperle. Dr. Lemperle, a cosmetic surgeon from Germany, worked closely with the manufacturer in the development of this injectable filler. His clinical experience with Artecoll is unsurpassed. Some highlights of these deliberations, particularly as they relate to potential untoward outcomes, are summarized below.

The two major adverse responses to injected Artecoll are early lump formation, which is fairly common, and later granuloma formation, which is quite unusual. The two are not always distinguishable on pathology because the pathologist will note the presence of a foreign body reaction in either case. Whereas early lumps or nodules are composed primarily of displaced polymethylmethacrylate (PMMA) microspheres, true "granulomas" are composed of perhaps 95% granulation tissue and only 5% microspheres. As a result, nodules are much firmer (and more difficult to inject) than granulomas.

Small lumps may occur for a period of time following Artecoll injection, particularly in the lips. Dr. Lemperle pointed out that if you observe women when they eat and speak, they tend to use their lips more than men, often with resultant radial lip line formation. He explained that injected Artecoll remains in a "paste" form for about 3 days prior to being fully encapsulated by host fibrin and fibrinogen. During this early postimplantation phase, lip movement associated with speaking, smoking, eating, and pouting can lead to displacement of the injected material, clumping of acrylic microspheres, and subsequent lump formation. For this reason, patients should be advised to minimize talking, chewing, and animated facial expressions for the first 3 days following Artecoll injection. Dr. Lemperle always advises patients that if they feel a lump or irregularity in the skin during this time, they can flatten it by massage.

Lemperle suggested that following injection of the lip, the area should be splinted with an external bandage of the lip and neck for 3 to 5 days until the implant has been stabilized. Obviously, this could result in some restrictions on social engagements. It was, therefore, suggested by one of the round table participants that perhaps pretreatment with botulinum toxin (Botox) by weakening the orbicularis oris muscle might result in less Artecoll displacement and associated formation of lumps in the lips. The consensus of the group was that this would be preferable to bandaging. One panelist pointed out that because the lip musculature generally responds to Botox within 2 or 3 days, one can perform both treatments (Artecoll and Botox) concurrently. Hopefully, future outcome studies will corroborate this impression. Another way to lessen the possibility of developing lip lumps following augmentation with Artecoll is to use only small amounts (one syringe) with each visit.

Injection of Artecoll into muscle can be problematic. By dynamic muscle movement, the PMMA particles may be dislocated and clumped together, producing a lump. This can, in particular, be a problem at the oral commissures, where there is very little fat between the dermis and the underlying musculature.

In general, early lumps following Artecoll injection can be expected to dissipate spontaneously over a 3-month period. Dr. Lemperle always advises patients that the final result of a treatment will not be evident for 3 months and that they should be prepared to have a few small lumps during that time.

Clinically, true "granulomas" can be differentiated from temporary lumps by the fact that the former appear at all injected sites at the same time, usually 6 to 24 months (but as late as 3 years) following injection. Paradoxically, according to Dr. Lemperle, who has tested a number of filler materials in his own forearms, those materials that incite the least amount of foreign body reaction appear to carry the greatest likelihood of subsequent granuloma formation.

The PMMA spheres in Arteplast, the forerunner of Artecoll, included many small surface impurities that are felt to have increased the likelihood of granuloma formation. These impurities adhered to the spheres as a result of electrostatic forces and resisted washing and sieve filtration. This processing problem was corrected, and, according to Dr. Lemperle, the incidence of granuloma formation has fallen dramatically since 1995, when the new, purified, injectable product was introduced. Nonetheless, the impression that Artecoll is associated with a high risk of granuloma formation persists, particularly among nonusers.

Artecoll has been available for 5½ years in Canada, with more than 60,000 syringes used. According to Canderm Pharma, Inc., the Canadian distributor of Artecoll, to date, 11 files have been reported, which equates to an adverse event rate of 0.018%. Of these 11 cases, 4 have been visually assessed as a granuloma (0.007%).

Granulomas, in Dr. Lemperle's experience, are self-limiting, resolving on their own in 4 to 6 years. Most patients prefer more timely resolution of these lesions if they occur, and intralesional Kenalog injections are quite effective in this regard. Lemperle reported that aggressive use of fairly high concentrations of Kenalog (up to 40 mg/mL concentration) early on seemed to have a lasting effect on keeping granulomas away. At this dosage, however, temporary indentations of the treatment site may occur. Intralesional corticosteroids tend to be more effective in treating true "granulomas" than in treating the much harder lumps or nodules that may occur in the early post-treatment period.

The actual cause of granuloma formation is still not known, but in 25% of Dr. Lemperle's 12 known cases, there was an antecedent infection of some type, months prior to the appearance of the granuloma. He advises that patients who develop a granuloma be questioned about previous infection. Previous trauma may also play a role.

I have had fairly extensive personal experience with Artecoll, injecting several hundred syringes since April 1998. During that time, I have encountered only one case of true granuloma formation. This was treated with monthly injections of Kenalog-10 Injection, with quite satisfactory results. Artecoll has most certainly been a welcome addition to my practice, and I encourage other clinicians to objectively explore this product's value.

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