
Discussion

Artecoll: A Long-Lasting Injectable Wrinkle Filler Material: Report of a Controlled, Randomized, Multicenter Clinical Trial of 251 Subjects

Discussion by Steven Fagien, M.D., and Trevor M. Born, M.D.

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In this article, Drs. Cohen and Holmes compare the safety and efficacy of Artecoll to the only long-term commercially available products for facial soft-tissue augmentation in the United States at the time of the study, Zyderm and Zyplast (bovine collagen). This study was a controlled, randomized, multicenter clinical trial for premarket approval with U.S. Food and Drug Administration guidance that for obvious reasons only permits comparisons with Food and Drug Administration–approved products. The choice of Zyderm and Zyplast was convenient, however, not simply because of the lack of any other prevailing options but also because the facilitating vehicle and dispersing agent contained in Artecoll is also bovine collagen at the same concentration as used in commercially available Zyderm I (35 mg/ml). One criticism of the design of the study is that the authors were unclear in this report about how the control, Zyderm II (65 mg/ml) or Zyplast (glutaraldehyde cross-linked bovine collagen at 35 mg/ml), was selected in each individual against Artecoll. Further inquiry revealed that in the control subjects, Zyderm II was used only in the glabellar region to reduce the possibility of any of the complications that have been associated with the use of Zyplast in this region.¹ Finally, although the use of bovine collagen might allow for a valid study and comparisons and removes some possible variables compared with other agents, it illustrates some of the problems inherent in using heterologous animal protein (allergy, the requirement for skin testing, and so on).^{2,3}

Although not discussed in this article, the choice of ingredients contained in Artecoll was not random. Through an apparently methodical approach in the search for a “permanent filler,” the ingredients in Artecoll were carefully selected.^{4,5} The choice of the alloplastic agent, polymethylmethacrylate, dates back to its proven track record of soft-tissue biocompatibility during World War II. The experiences with the apparently well-tolerated ocular penetrating injuries with retained intraocular foreign bodies of fighter pilots hit by projectile shattered Perspex windshields evolved into its use as a component in intraocular lenses implanted after cataract surgery for vision restoration.⁶ (Perspex was later commercially manufactured as Plexiglas, a form of polymethylmethacrylate.)

The inclusion of bovine collagen was also not simply an accident or a matter of convenience. It has been shown that collagen “fibers” disperse (separate the particulate spheres to avoid “clumping”) the polymethylmethacrylate better than any other vehicle.⁷ As briefly mentioned in the article, the use of agents not quite as effective in dispersing the alloplast (such as the gelatin used in Arteplast) has been shown to cause problems with particle clumping. Although the overall safety and efficacy have been established, the question still remains as to whether bovine collagen is the best dispersing agent. If it isn’t, what would otherwise be the ideal agent for polymethylmethacrylate dispersion? In addition, what other advantages could be derived with the use of an alternative dispersing agent (such as human allogeneic collagen) that would obviate all of

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the disadvantages of heterologous collagen and avoid a skin test.³

It is also only too common that agents go through an evolution of purification and product optimization that is only discovered after (sometimes years of) experience. Dermalogen,³ Restylane,⁸ Hylaform,⁹ and even Botox are all products that are commercially available in the United States that had problems relating mostly to "impurities" (including nonactive proteins) that were discovered and then rectified to make the product safer. The evolution of product improvement relates to Artecoll as well. The reduction of microscopic surface irregularities and the smaller particle size have been said to enhance its safety and efficacy.⁵

The results of this study clearly show a definite improved efficacy of Artecoll over Zyderm and Zyplast. Should we be surprised at this? The search continues for the "ideal filling agent" with characteristics that include, but are not limited to, safety, persistence, and aesthetics. As the product ingredients have been shown to be highly safe and biocompatible, as with most injectable agents, the complications (other than "reactions" to any of the components of the product) usually reflect injection technique and issues that are "proximal to the syringe." The incidence of adverse events in this study parallels our experiences and observations and is surprisingly low, oftentimes indicating a higher level of experience and expertise as well as experience-influenced conservatism and caution. There is also experience-influenced bias regarding the threshold for what is considered an adverse event rather than an anticipated sequela. Our collective experience (which has been mostly through the experience of Dr. Born) includes more than 3000 patients since 1998, when Artecoll was approved in Canada. In our experience, only one patient had an apparently positive skin test (unusually low), and none of our patients exhibited the occasionally reported painful nodules or granulomas. Although it is common that some incidents go unreported, Canderm Pharma, Inc., the Canadian distributor of Artecoll, has only four reported cases of possible granulomas (by visual assessment only; biopsies were not performed) and seven other adverse events (data on file).¹⁰ Artecoll has been available in Canada for nearly 6 years and approximately 60,000 syringes have been distributed. This would represent an adverse event rate of 0.018 percent in Canada.

Also in our experience, five patients were treated for "irregularities" caused by injections that were administered more than 3 years earlier. All of these irregularities were due to injections into the lip region. In the first two patients, problems resulted from the injection of an abundance of material into one portion of the red lip; in one of these patients, a 3-mm "clump" (aggregate) of polymethylmethacrylate was excised without deformity. A third patient developed an irregularity (asymmetry, with obvious focal area of augmentation) of the vermilion border that was corrected by injecting additional Artecoll into the vermilion adjacent to the irregularity. A fourth individual (who was initially lost to follow-up) presented with a similar irregularity of the vermilion border 1.5 years after initial treatment. This was successfully treated with ultra-diluted triamcinolone injections and Botox (botulinum toxin type A) to the lips; a good response was achieved.

The case of the fifth individual is actually most applicable to this article. This patient received Artecoll injected focally into multiple vertical lip lines. A satisfactory result was obvious to the injector and patient for the first several months. As the focal soft-tissue edema resolved (presumably after the bovine collagen had completely dissipated), the Artecoll could be seen in the individual lines and was particularly noticeable when the patient placed the lip under tension over the teeth (i.e., when smiling). This was treated by precise intraoral/transmucosal excision of the polymethylmethacrylate; a good long-term result was achieved. It has clearly been our experience that for treatment of the lips, the material needs to be placed deeper than in other facial regions. Even greater safety and precision can be facilitated by partially immobilizing the region with tape and Botox to minimize migration, clumping, and other contour abnormalities. Injection of individual fine lines should also be done with extreme care, as the irregularities and visibility of the material that may result can be quite difficult to correct. It has also been our experience and the experience of others that treatment of crow's feet is met with similar concerns. Finally, with regard to treatment of the lips, especially for augmentation, when the material is placed along the mucosa (abutting the teeth), the patient may palpate a significant disconcerting nodularity with his or her tongue. This is difficult to avoid at times, especially when attempting to in-

crease lip projection. Due to a greater incidence of problems related primarily to the lip region with the current techniques, the Food and Drug Administration will presently not endorse its use for this application/region.¹¹

Interestingly, in this article there appeared to be some surprise regarding the nearly equivalent efficacy of Artecoll and Zyderm in the glabella region. This might be explained in part by the conservative approach of experienced injectors who were either personally or peripherally aware of problems related to treatment to this region, including the potentially devastating complications of necroses and even blindness.^{1,12} Although these complications have been reported only sporadically with other agents (mostly bovine collagen and fat), the extent of this potential morbidity frightens even the most experienced injectors. I believe, however, that this, too, is likely related to injection technique and less to the particular product used.

In general, three salient issues should be considered when entertaining treatment with any injectable agent, including Artecoll: (1) the location and configuration of the region to be treated; (2) the appropriate depth (placement) of treatment (injection); and (3) the volume of material placed. More mobile areas are destined for more displacement of the material. A deeper plane of injection is likely to herald far fewer problems regarding visibility of the agent while augmenting the soft tissue. Generally, the goal should be to correct a fold with approximately 50 percent improvement followed by reassessment after a period of time to evaluate the response. We must also consider the performance of the agent and anticipate the patient's experience. For example, in the treatment of the nasolabial fold as shown in Figure 8 of the article, what should also concern us that may not be evident in standard clinical photographs? Note that there is near-complete correction of this contour defect. From the patient's perspective, although improved aesthetically (photographically) in repose, this region may appear or feel very stiff and resistant with animation (smiling). Also, over time the fold may migrate and new folds (i.e., at the corner of the lip) may develop due to tissue pressure and the stiffness of the adjacent nasolabial fold, and so on. Unlike with nonpermanent fillers, the persistence will make Artecoll far more technique-sensitive, as errors can be long lasting if not permanent.

In summary, we congratulate Drs. Cohen and Holmes for their efforts not only in proving a superiority in persistence (efficacy) of Artecoll compared with bovine collagen but also in sharing their philosophies, difficulties, and recommendations so we can benefit from their experiences. As with many currently available agents, there is a continuous effort for product optimization, as we believe the product can be rendered safer and more user- and patient-friendly by establishing clear treatment guidelines (and relative exclusions) and perhaps substituting the carrier vehicle with the most effective agent that would also avoid a skin test. As the biocompatibility, persistence, and performance of polymethylmethacrylate have been established (here and in other studies), it is our opinion that, as with all products, a higher level of understanding of the properties of this agent, the facial regions that are most appropriate for treatment, and the best injection technique will deliver the most satisfactory results.

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