ORIGINAL ARTICLE

Facial soft tissue augmentation with Artecoll®: A review of eight years of clinical experience in 153 patients

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OBJECTIVE: Artecoll (Canderm Pharma Inc, Canada) is a semipermanent, injectable, soft tissue filler composed of uniform polymethylmethacrylate microspheres in a bovine collagen gel, which has been used in Europe over the past decade. The authors review their experience using Artecoll as an injectable material for the correction of deep static folds of the face, improvement of nasal asymmetries following rhinoplasty, depressed acne scars and augmentation of the lip.

METHOD: A retrospective chart review, subjective patient satisfaction feedback and objective findings noted by the senior author were performed over an eight-year period. A total of 153 patients were treated with Artecoll injections; 74 underwent lip augmentation, 21 underwent deep nasolabial fold augmentation, eight underwent glabellar fold augmentation, 26 were treated for minor nasal dorsal irregularities and 24 were treated for depressed acne scars.

RESULTS: No early or delayed allergic responses were reported. Complications occurred most commonly with lip augmentation, in which 13.5% of patients noted significant noticeable bruising postinjection that resolved completely within one week, 51.3% had detectable implant on palpation, and 13.1% required further intervention with massage, steroid injection and/or local excision to correct for lumpiness. Sixty per cent of patients requiring further intervention responded successfully, while local excision was performed on the two patients who failed to respond after six months of massage and steroid therapy. Overall, a total of 11 patients (14.9%) had minor asymmetries or less than optimal results within the lip augmentation study group. Among other sites, the most common complaint was undercorrection of the fold or wrinkle.

CONCLUSION: Based on the authors' experience, Artecoll is a safe, viable option for long-term treatment of deep facial wrinkles, nasal asymmetry, hypoplastic or atrophic lips, and depressed acne scars, and the results have been accompanied by a high degree of patient satisfaction. Although the implant is often palpable, rarely does it cause significant visible lumps. Its use and applications as a semipermanent injectable agent certainly warrant further investigation.

Key Words: *Artecoll; Dermal filler; Soft tissue augmentation*

L'augmentation des tissus mous du visage à l'aide d'Artecoll® : l'analyse de huit ans d'expérience clinique auprès de 153 patients

OBJECTIF : L'Artecoll (Canderm Pharma Inc, Canada) est un produit de comblement des tissus mous semi-permanent et injectable composé de microsphères uniformes de polyméthacrylate de méthyle dans un gel de collagène bovin, qui est utilisé en Europe depuis dix ans. Les auteurs analysent leur expérience de l'Artecoll utilisée comme matière injectable pour corriger les profondes rides statiques du visage, améliorer les asymétries nasales après une rhinoplastie, combler des cicatrices d'acné en creux et augmenter les lèvres.

MÉTHODOLOGIE : Les chercheurs ont procédé à une analyse rétrospective des dossiers, ont obtenu les commentaires subjectifs sur la satisfaction des patients et colligé les constatations objectives consignées par l'auteur principal sur une période de huit ans. Au total, 153 patients ont reçu des injections d'Artecoll : 74 ont subi une augmentation des lèvres, 21 une augmentation du pli nasolabial profond et huit une augmentation des rides glabellaires, tandis que 26 ont été traités en raison d'irrégularités mineures de l'arête du nez et 24, de cicatrices d'acné en creux.

RÉSULTATS : Les chercheurs n'ont constaté aucune réponse allergique précoce ou tardive. Les complications s'associaient surtout à l'augmentation des lèvres, à l'égard de laquelle 13,5 % des patients ont remarqué une ecchymose très perceptible après l'injection, qui se résorbait tout à fait au bout d'une semaine, 51,3 % avaient des implants décelables à la palpation et 13,1 % avaient besoin d'une intervention supplémentaire par massage, injection de stéroïdes ou excision locale pour corriger une bosse. Soixante pour cent des patients qui avaient besoin d'une intervention supplémentaire y ont réagi de manière positive, tandis que deux patients ont subi une excision localisée parce qu'ils n'avaient pas répondu à six mois de massages et de stéroïdothérapie. Dans l'ensemble, 11 patients (14,9 %) présentaient des asymétries mineures ou des résultats sous-optimaux dans le groupe d'étude ayant subi une augmentation des lèvres. Dans les autres foyers d'injection, une correction insuffisante du pli ou de la ride était la principale doléance.

CONCLUSION : Selon l'expérience des auteurs, l'Artecoll est une option sécuritaire et viable pour le traitement à long terme des profondes rides faciales, de l'asymétrie nasale, des lèvres hypoplastiques ou atrophiées et des cicatrices d'acné en creux, et les résultats s'accompagnent d'une profonde satisfaction de la part des patients. Même si l'implant est souvent palpable, il cause rarement des bosses visibles importantes. Son utilisation et ses applications sous forme d'agent injectable semi-permanent méritent des recherches plus approfondies.

Injectable collagen has a longstanding reputation for being used as a temporary soft tissue filler in nonallergic patients. Artecoll (Canderm Pharma Inc, Canada), also marketed as Artesense (Canderm Pharma Inc, Canada) and ArteFill (Canderm Pharma Inc, Canada), is an injectable implant consisting of two components commonly used in both aesthetic and reconstructive surgery: bovine collagen, and microspheres of polymethylmethacrylate (PMMA). They account for 75% and 25% of Artecoll's composition, respectively (1-3). PMMA has been used extensively in dental and orthopedic surgical settings, largely as a biocompatible cement (4,5). In addition, a trace amount of lidocaine is included in Artecoll's formulation to help assuage local discomfort during injection.

The ultimate goal in treating deep skin creases is to expand dermal layer volume and simultaneously replace dermal collagen (6). In Artecoll, bovine collagen functions as a transient carrier of PMMA microspheres, and facilitates their deposition in tissue. The goal of depositing PMMA microspheres in tissue is to elicit a fibrotic process resulting in the formation of microcapsules around each PMMA microsphere. The viscosity of the collagen carrier molecule enables the even distribution of the microspheres in the tissue, thereby promoting tissue ingrowth between the microspheres. As such, a more permanent tissue filling or augmentation is achieved (7).

Artecoll is the only United States Food and Drug Administration-approved permanent injectable filler for nasolabial fold augmentation

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(8). It has numerous clinical applications including the correction of unwanted facial wrinkles, facial volume augmentation, effacement of acne scars and injection rhinoplasty. The largest experience of Artecoll use is in Europe, where it has appeared to be a viable, permanent tissue filler with minimal complications in comparison with other forms of tissue fillers (1-3). In the present article, we review our experience with the efficacy of Artecoll as a soft tissue injectable implant in the following five clinical scenarios: lip augmentation; deep nasolabial folds; static glabellar grooves; postrhinoplasty dorsal irregularities; and depressed facial acne scars.

METHODS

A retrospective chart review, along with subjective patient satisfaction feedback and objective findings noted by the senior author, was performed. Patients seeking cosmetic improvements for deep glabellar grooves, prominent nasolabial folds, atrophic lips, postrhinoplasty dorsal asymmetries or depressed acne scars were treated with Artecoll. Before treatment, all patients were screened for previous collagen use and history of reaction to collagen products. Patients without a history of collagen use were offered a collagen skin test. Only 10 patients in the study group elected to undergo bovine collagen allergy skin testing on the volar aspect of their arm, and they were re-inspected after four weeks for evidence of allergic reaction. If tolerated, the specific areas of cosmetic concern were addressed. All risks of allergy were disclosed and the patient's informed consent was obtained. All study patients met the following inclusion criteria: current treatment of only one individual aesthetic unit; no history of injection with semipermanent or permanent filler before this treatment; and not receiving adjunct therapy with the exception of Botox (Allergan, Canada) injection in the subgroup treated for glabellar lines. Exclusion criteria included patients with a history of collagen allergy or collagen vascular disease. Exclusions also included patients with well-known contraindications to Artecoll use, including patients who were pregnant, lactating, or those with a history of hypertrophic or keloid scar formation (5).

The authors' method of Artecoll injection is similar to that described elsewhere (1). Xylocaine 1% without epinephrine was used as a local anesthesia field block before Artecoll injection for lip augmentation; ice was applied to all other facial injection sites. The Artecoll syringe was thawed before injection. As the injection was performed, the needle bevel was directed downward to help ensure filler deposition into a deeper plane. Steady pressure was applied to the syringe during injection, and the implant was placed appropriately to achieve the aesthetic goal. With each passage of the needle, small tunnels in the tissue were formed, thereby creating space for the deposition of Artecoll. If great resistance was encountered during injection, the needle was withdrawn and replaced with a new needle to avoid the potential for uncontrolled delivery of the tissue filler boluses.

During the injection, the objective was to raise the fold to a height equal to that of the peripheral skin surface. To achieve this goal while avoiding overcorrection, the specific fold and a border of a few millimetres on each side of the fold was injected. Subsequently, fingertip massage was performed to facilitate a more even distribution of the substance. Afterward, patients were instructed to apply cold compresses to the area for comfort.

In the lip augmentation subgroup, the location of Artecoll injection varied depending on the desired effect. To avoid distortion of the red lip, field blocks of the gingivobuccal sulcus and a mental nerve block were performed before injection of the upper lip and lower lip, respectively. To improve atrophic vermillion borders, Artecoll was deposited in multiple tunnels parallel to the vermillion at the subcutaneous level. To achieve eversion off the incisors and added projection, the wet line was injected subcutaneously. To obtain a lip with greater body, Artecoll was placed into the mid-lip. Finally, massage was performed to improve contouring. As with facial fold rectification, the ultimate goal was even correction rather than overcorrection.

Asymmetry of the nasal dorsum following rhinoplasty was corrected with Artecoll injection in a subset of patients who underwent rhinoplasty surgery a minimum of 12 months previously. Patients were considered to be candidates if they had isolated, subtle, nasal bone asymmetry and declined a secondary surgical rhinoplasty procedure. It was believed that Artecoll was safest when injected directly on the nasal bone in the correction of dorsal imperfections resulting from osteotomies. As such, Artecoll was used only to correct irregularities of the superior one-third of the nose.

For treatment of depressed acne scars, Artecoll was used as an isolated modality or in conjunction with carbon dioxide laser resurfacing procedures.

Consideration of whether subsequent Artecoll injection was necessary followed a waiting period of approximately four months. Because Artecoll was used mainly for static lines, patients with a significant component of dynamic folds in the glabellar region were additionally given Botox injections, simultaneously or sequentially. All patients were followed for a minimum of two years from injection.

RESULTS

Over an eight-year period, a total of 153 patients were injected with Artecoll; 74 underwent lip augmentation (48.3%), 21 underwent nasolabial fold augmentation (13.7%), eight underwent glabellar fold augmentation (5.3%), 26 underwent treatment of dorsal irregularities following rhinoplasty (17.0%) and 24 underwent depressed acne scar modification (15.7%). None of the patients treated demonstrated allergic response during Artecoll preinjection testing. The mean postinjection follow-up period was 34 months, and ranged from 24 to 84 months. All patients were reviewed at a minimum of three months postinjection, at which time subjective and objective analysis of cosmetic results were obtained. Of the 153 patients, 12 (7.8%) expressed less than complete satisfaction with Artecoll, while 141 (92.1%) reported overall satisfaction with Artecoll (Table 1).

Lip augmentation

Of the 74 patients receiving injections in the lip augmentation subgroup, 19 patients (25.7%) had upper lip only, 11 patients (14.9%) had lower lip only, and 44 patients (59.4%) had combined upper and lower lip (Table 2). Thus, a total of 118 lips required injections, of which 108 (91.5%) required only one vial of Artecoll. The remaining 10 lips (8.5%) required up to two vials. Accordingly, three of the 10 patients requiring two vials had their second injection three months after the initial treatment. Patients experienced mild discomfort during injection and in the immediate postinjection period. Sixty-eight of the 74 patients (91.9%) reported complete satisfaction with the outcome of their lip augmentation.

Artecoll appeared to be a semipermanent filler, maintaining good volume on subsequent follow-up for a minimum of two years in all patients. This was determined via subjective patient satisfaction and objective evaluation. On palpation, the areas injected with Artecoll appeared to blend into surrounding tissues smoothly in most patients. However, a lip texture characterized by localized lumpiness suggestive of implant augmentation was detected in 52 individuals, but only five of these patients (9.6%) reported awareness of the implant. Visible lump formations or significant palpable lip deformities were treated with massage and triamcinolone steroid injection. These measures failed in two patients, who subsequently underwent excision of the palpable lip defect under local anesthesia. No sequelae resulted.

Deep nasolabial fold augmentation

Of the 21 patients who underwent augmentation of their nasolabial folds, two patients required unilateral injection. Accordingly, 40 nasolabial folds were filled. In total, 13 folds (32.5%) required one vial of Artecoll, 23 folds (57.5%) required two vials, and four folds (10%) required three vials. A significant number of nasolabial folds required up to two vials for satisfactory improvement of the folds at the initial injection. Subjectively, deep nasolabial lines did not respond as well as mild to moderate lines. While maintaining good volume over time, the implants did not exhibit unnatural induration or nodularity to palpation. Overall satisfaction with nasolabial fold augmentation was

TABLE 1
Anatomical injection site, number of patients receiving Artecoll* and number of patients satisfied with the treatment

	Injection site				
	Lips	Deep nasolabial fold	Glabellar fold	Dorsum of nose	Depressed acne scar
Patients, n	74	21	8	26	24
Satisfied, n	68	18	6	26	23

**Canderm Pharma Inc, Canada*

reported by 18 of the 21 patients (85.7%). The three patients who were not fully satisfied (14.3%) all conveyed that there was some improvement with treatment, but they desired a more significant change. These patients had deferred additional treatment. Of the four patients who had a total of three vials, three patients were initially treated with two vials and received a third vial three months later. Of the three dissatisfied patients, two were injected with one vial and one had two vials injected. Two of the three patients were described as having moderately deep folds and one was described as having severe folds. It was believed that these patients were undercorrected and further augmentation could be obtained with additional filler.

Static glabellar groove augmentation

A total of 14 glabellar folds in eight patients were injected, all of which required, on average, less than one vial for complete treatment. In four patients with excessive muscular activity causing prominent dynamic frown lines, the glabellar region was treated adjunctively with Botox injection two weeks before the Artecoll injection. Six of the eight patients (75%) expressed satisfaction with the Artecoll injection. The two patients who were not completely satisfied had persistent linear lines into the dermis, which were not effaced completely by Artecoll.

Postrhinoplasty dorsal irregularities

Twenty-six patients were treated for minor asymmetries of the nasal dorsum postrhinoplasty after a minimum period of 12 months following surgery. These patients were all offered secondary surgery or filler to correct minor imperfections of their nasal dorsum. All of these patients had an isolated dorsal irregularity and did not wish to undergo a secondary rhinoplasty surgery. On average, 0.2 mL of product was used in each patient. All patients (100%) in this group were satisfied with treatment.

Depressed acne scars

A total of 24 patients were treated with Artecoll for depressed acne scars. Twenty-three of the 24 patients (95.8%) noted significant subjective improvement of their acne scars postinjection. Nine of the 24 patients (37.5%) noticed a palpable textural change to their skin from the injection. None of the patients had significant granuloma formation or visible lumpiness. Twenty-one of the 24 patients (87.5%) were treated with a single vial of Artecoll while the remaining three patients were treated with two vials. The second treatment was performed three months after the initial treatment. Six of the patients (25.0%) elected to undergo laser resurfacing procedures as a secondary treatment modality for their acne scars.

DISCUSSION

In Artecoll, the PMMA microspheres are suspended in a gel of bovine collagen. The collagen functions to smoothly deliver and evenly disperse the PMMA microspheres, and is eventually resorbed. Artecoll, specifically, has been used in Europe for nipple reconstruction, tear trough or naso-orbital grooves, and chin augmentation (1). Another reported use for Artecoll was injection laryngoplasty to successfully treat glottic insufficiency secondary to unilateral vocal fold motion impairment (9). The most extensively documented clinical experience with Artecoll as a skin and soft tissue filler has been in Europe, where

TABLE 2
Anatomical subsite analysis for lip injections

	Upper lip	Lower lip	Upper and lower lips
Patients, n	19	11	44

it has been used for more than 10 years. Lemperle et al (1,2) treated 2000 patients for static lines and lip augmentation and prospectively reported on the initial 100 patients. At the five-year follow-up, 90% of patients were satisfied with their results; fewer than 2% expressed dissatisfaction (1,2).

Artecoll's main limitations include its high cost and its tendency to result in lip lumpiness. Placement of Artecoll in locations with thin skin, such as the periorbital region, should also be performed with caution (10). The indications and limitations of the product, as well as the possible need for adjunct therapies to achieve optimal results, must be stressed to patients. According to European Artecoll data, approximately 50% of patients may require a second Artecoll treatment to achieve desired results (7).

It has been suggested that developing nodules or ridges, or having visibly noticeable implants, are associated with the experience and expertise of the physician administering the injection (10). The role of massage in preventing lump formation has been previously suggested (5). Some surgeons recommend using lip massage for the first few days after injection to spread Artecoll evenly within the subcutaneous space and to avoid lump formation from poor initial technique. Others believe that there is a propensity for lump formation resulting from orbicularis oris activity pushing the implant into clumps, similar to pearl formation. Therefore, massage may counteract orbicularis oris contraction and reduce lumpiness. Finally, there have been suggestions that the adjunct use of low-dose Botox injected into the orbicularis may reduce the clumping of Artecoll and, therefore, be useful to prevent lumpiness (5). These aforementioned theories are speculative and require further evaluation.

Acute complications, which have been previously reported elsewhere and noted in some of our patients, included echymoses and erythema, which lasted a few days, and itching, which can require several weeks to resolve. None of our patients experienced an allergic reaction. The delayed complication of lump formation was noted in 13 patients (8.50%), all of whom had undergone lip augmentation. Palpable implants do not appear to be a problem after treatment of folds or dorsal nasal irregularities.

The uniform size, purity, and smooth, polished surface of the PMMA microspheres prevent phagocytosis by macrophages (7). As a result, the incidence of PMMA microsphere-induced granulomatous reactions is rare. No patients in our series formed granuloma. Only 10 cases of granuloma formation have been reported to the manufacturer since its introduction in Europe in 1993 (10,11). Scanning electron microscopy analysis of five different PMMA soft tissue fillers, including the 2005 version of Artecoll and the 2007 version of Artefill, revealed particle sizes ranging from 30 µm to 50 µm, with a negligible number of particles of smaller sizes; the microspheres had smooth surfaces with only minimal irregularity and scant, if any, sediment (10). Variability exhibited by surface analysis in the scanning electron microscopy analysis was attributed to affect migration, and has been previously documented (5,12). Particles with a higher percentage of particles smaller than 20 µm in diameter are believed to encourage phagocytosis and, thus, adverse events (13). Histological studies demonstrate that over a two- to three-month period, the collagen is phagocytosed and degraded by macrophages and replaced by host collagen laid down by fibroblasts (7). This fibrotic tissue essentially is composed of multiple small capsules surrounding each individual PMMA sphere, analogous to the capsule surrounding breast implants. The maintenance of tissue filling is attributed to this mesh of fibrous capsular tissue encompassing these colonies of microspheres. Based on serial histological specimens and computerized calculations, it is estimated that 75% to 100% of the initial injected

volume is maintained, and this volume becomes stable indefinitely at approximately four months. Long-term follow-up of up to four years demonstrates no significant change in tissue volume. Additionally, rounder particles are more apt to resist phagocytosis (5).

The multitude of soft tissue fillers used for wrinkle effacement and tissue supports the belief that the ideal tissue filler does not exist (14-18). The quintessential tissue filler should be easy to administer, nonimmunogenic, biocompatible, predictably permanent, identical in texture to surrounding tissue and affordable. The disadvantage to most biological fillers is resorption over time. Hyaluronic acid fillers function well; however, their lifespan ranges from four up to 18 months (18). Similarly, bovine collagen filler disappears with time, thereby necessitating periodic injection (18). Additionally, a small percentage of patients are not candidates for this filler secondary to allergic reaction to bovine collagen. The product is also contraindicated in pregnant or lactating women, and in patients with a history of keloid or hypertrophic scar formation (6). While homologous collagen fillers such as Alloderm (LifeCell, USA), derived from processed human dermis, also resorb with time, a certain volume of tissue remains secondary to replacement by host tissue. In lip augmentation, Alloderm can leave a palpable and visible implant. Autologous fat injection requires both harvesting and processing of fat, and subjects the donor site to small yet not insignificant risks. Despite reports of autologous fat injection approaching 100% survival, the majority of clinicians note unpredictable fat graft survival and do not consider fat injection to be a permanent filler (14,16). In anticipation of resorption, both fat and collagen injection as well as Alloderm placement require the operator to overcorrect, resulting in a period of visible patient swelling that is difficult to camouflage.

Although permanent, injectable allograft implants such as silicone can subject patients to chronic inflammation, and often leave tissue with an unnatural appearance and texture (1). Oil-based silicone injections may have a greater tendency to spread beyond the intended areas of treatment. Moreover, it is difficult to reverse the effects of silicone injection and, thus, should be used with caution. Injectable silicone is currently prohibited in Canada.

Gortex, used in lip augmentation or in the effacement of nasolabial folds, enables in-growth of host tissue; however, it often remains palpable and unnatural in texture. Occasionally, gortex can leave visible margins. Finally, the use of gortex for small defects is less practical than the use of semipermanent or permanent injectable products.

Acrylic hydrogels have been used as an alternative semipermanent injectable. Products such as DermaLive (Derma-Tech, USA) and Dermadeep (Derma-Tech, USA) are composed of hyaluronic acid and acrylic material. Hyaluronic acid constitutes 60% of the formulation, and functions as the carrying fluid vector for the acrylic. Because these products do not contain collagen, no allergy testing is required. They have been used in Europe since 1998 and requires careful evaluation of its results (19). Case reports of severe granuloma formation with secondary bacterial infection after DermaLive injection have been documented (20). It has been suggested that the incidence of severe adverse reactions, such as nodule formation following DermaLive injection, is likely higher than with biodegradable fillers, and may relate to its irregularly shaped surface (21). Additionally, there may be a latency of up to two years (20). This product was removed from the Canadian market in 2008, and a class-action lawsuit has been filed.

There have been a number of long-lasting or semipermanent injectable fillers on the market over the years in Canada. Overall, our experience indicates that Artecoll, a semipermanent injectable filling agent, appears to have high patient satisfaction. In our series, Artecoll had an acceptable patient safety profile and an extremely high satisfaction for soft tissue augmentation of facial folds and correction of minor nasal asymmetries postrhinoplasty. The product was considered to provide good long-term correction of atrophic lips. Although Artecoll frequently caused palpable textural change in patients who underwent lip augmentation, only a small minority was severe enough to warrant steroid injection or surgical intervention. Artecoll is the only semipermanent product that has withstood the test of time, as other, competitive, semipermanent products have caused significant local complications and have been removed from the market. It is worthwhile offering Artecoll treatment in one's practice to serve patients seeking semipermanent to permanent lip enhancement, treatment of facial folds, correction of subtle rhinoplasty nasal bone asymmetries and the correction of depressed acne scars with long-lasting results. Physicians administering Artecoll injection must have experience with its use and inform the patient of the relatively high possibility of developing palpable textural change at the injected site, especially the lip area.

While Artecoll carries higher risks than temporary fillers, such as hyaluronic acids, it still provides a safe and effective alternative in facial aesthetic surgical practice when used with care. Artecoll can act as a specific and unique tool for permanently enhancing subtle nasal bone asymmetries in postrhinoplasty patients, and provide permanent improvement of depressed acne scars, permanent lip enhancement and permanent correction of facial folds.

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