A Report on the Safety of and Satisfaction With Particle-Based Fillers, Specifically Polymethylmethacrylate Microspheres Suspended in Collagen

Alain Dansereau, MD; Douglas Hamilton, MD; Angelica Kavouni, MD; Constance Neuhann-Lorenz, MD; Sheldon Pollack, MD; Robert Richards, MD; Marie-Christine Roy, MD; Peter Rullan, MD; Christine Tang, MD; Arie Benchetrit, MD

This report covers survey results and discussions of the safety of polymethylmethacrylate (PMMA) fillers. The results presented are from a recent survey of 1032 patients on their satisfaction with Artecoll (the first PMMA dermal implant). The data show a high level of patient satisfaction from 1993 to 2007. There has been speculation and controversy about the safety of permanent and semipermanent particle-based fillers. The authors, selected for their long-term experience with these fillers, discuss the use of particle-based PMMA fillers (Aphrodite Gold, Artecoll, ArteFill, and ArteSense). The safety profiles and potential preventive measures of side effects of PMMA fillers are reviewed. Treatment methods for granulomas, which occur rarely—in fact, only 9 patients experienced granulomas out of 18,472 syringes injected by the group—are also described. There was consensus that extensive training is imperative to achieve successful patient outcomes.

Dr. Dansereau is Dermatologist, private practice, Repentigny, Quebec, Canada. Dr. Hamilton is Dermatologist, private practice, Beverly Hills and Woodland Hills, California, and Assistant Clinical Professor of Dermatology, David Geffen School of Medicine at UCLA. Dr. Kavouni is Plastic Surgeon, private practice, and at Chelsea and Westminster Hospital, London, United Kingdom. Dr. Neuhann-Lorenz is Plastic Surgeon, private practice, and at Krankenhaus des Diakoniewerkes and Ambulantes Operationszentrum München-Nord, Germany. Dr. Pollack is Dermatologist, private practice, and Associate Professor of Medicine, Univeristy of Toronto, Ontario, Canada. Dr. Richards is Plastic Surgeon, Associate Professor of Plastic Surgery, and Director, Residency Training Program, Division of Plastic Surgery, Department of Surgery, University of Western Ontario, London, Canada. Dr. Roy is Dermatologist, private practice, Saint-Lambert, Quebec. Dr. Rullan is Dermatologist and Medical Director, Dermatology Institute, Chula Vista, California, and consultant, Scripps Mercy Hospital and Sharp Memorial Hospital, Chula Vista. Dr. Tang is Plastic Surgeon, private practice, Toronto. Dr. Benchetrit is Plastic Surgeon, private practice and Lakeshore General Hospital, Pointe-Claire, Quebec.

The First World Polymethylmethacrylate Expert Summit and the survey on patient satisfaction were sponsored by Canderm Pharma Inc and Fame Medical Products BV (aap bio implants group).

Dr. Dansereau is part owner of Artes Medical, Inc. Dr. Hamilton is part owner of and a consultant for Artes Medical, Inc. Dr. Pollack is a speaker for Canderm Pharma Inc. Dr. Richards provides training for Canderm Pharma Inc. Dr. Rullan is part owner of Artes Medical, Inc. Dr. Tang is a consultant for Canderm Pharma Inc.

Presented in part at the First World Polymethylmethacrylate Expert Summit, June 10, 2007, Miami, Florida.

In the first half of 2007, a survey of patient satisfaction with Artecoll (polymethylmethacrylate [PMMA]) was conducted in Canada and Europe. Patients from 6 physicians, who volunteered to participate, were asked to answer an institutional review board–approved questionnaire related to their experience with Artecoll. The response rate was high (52%), and the results were similar in both populations (except for the lip indication). Combined results (Canada and Europe) are presented in Tables 1 through 4. One thousand thirty-two patients responded to the survey. Approximately 40% of the treatments occurred between 1993 and 2004, inclusive, and 60% between 2005 and early 2007. Overall, more than 80% of the patients, regardless of the question, expressed a positive opinion about the results, their personal satisfaction, and their desire to recommend the product. The most frequent indications treated were nasolabial folds (32%), marionette lines (24%), the lips (18%), and the glabella (16%). It is interesting to note that the lips corresponded to more than 33% of the indications treated in Canada but only 5% of the indications in Europe. Less than 20% of the patients reported side effects, the most frequent of which were bruising, lumps, and swelling. No cases of granuloma were reported in this survey.

TABLE 1

Artecoll Surveys: Population Profile and Response Rate

Population Profile	Response Rate
Participating physicians, no.	6
Surveys distributed, no.	1989
Responses received, no.	1032
Response rate, %	52
Female respondents, %	94
Male respondents, %	6
Average age at time of survey, y	53
Treatments from 1993–2004, %	40
Treatments from 2005–early 2007, %	60

TABLE 2

Artecoll Surveys: Patient Satisfaction

Survey Question	Patients Responding, %
Do you still see results?	Yes: 80 No: 20
Overall, are you satisfied with the Artecoll treatment?	Yes: 84 No: 16
Would you do this treatment again?	Yes: 83 No: 17
Would you recommend this treatment?	Yes: 84 No: 16

BACKGROUND AND HISTORICAL PERSPECTIVE

Modern dermal fillers have been on the market for decades.[1] Their composition has evolved, but the variety

TABLE 3

Artecoll Surveys: Indications Treated

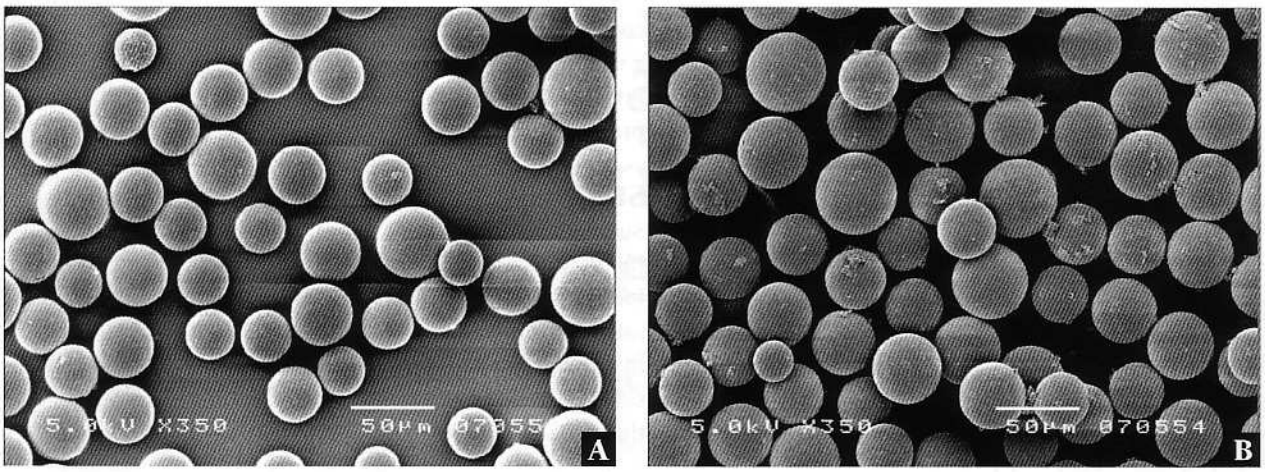
Indication	Treated, %
Nasolabial folds	32
Marionette lines	24
Lips	18
Glabella	16
Others	10

TABLE 4

Artecoll Surveys: Side Effects After Treatment

Patient Reports	Patients, %
No side effects	81
Side effects	19
Most frequent side effects*	
Bruising	6
Lumps/bumps/ridges	4
Inflammation/swelling	3
Tenderness	2
Redness	1

*No cases of granulomas were reported in the survey.



Manufacturer's specifications of ArteSense/Aphrodite Gold are microspheres' diameter 32–40 µM, polymethylmethacrylate microspheres <20 µM (<1% by number)(A). Specifications of ArteFill are microspheres' diameter 30–50 µM, polymethylmethacrylate microspheres <20 µM (<1% by number)(B).

of material used remains either from biological origin, synthetic origin, or both. Whereas some dermal fillers consist solely of viscous liquids, others may also contain suspended particles. The US Food and Drug Administration (FDA) classifies fillers as either volumizers or stimulators.[2] The particle-based PMMA filler is considered a stimulator because it stimulates the production of collagen rather than exclusively providing immediate volume. In 1989, 85 years after PMMA was first synthesized, Arteplast, the first PMMA particle-based dermal filler, was used in a clinical study. Artecoll, the second generation of Arteplast, was launched in 1993 in France, and, by 1998, it was approved in Canada. In 1997 and 1998, an FDA phase 1 clinical trial was performed in the United States[3]; in 2001, an FDA phase 3 clinical trial with Artecoll was successfully completed in the United States. In 2003, following the recommendations of the FDA, the specifications of the PMMA smooth spheres were reduced to less than 1% by number of particles smaller than 20 µM. Today, ArteSense, Aphrodite Gold, and ArteFill meet these FDA requirements (Figure). In fact, the range of the specifications for the diameter of the microspheres for ArteSense and Aphrodite Gold (32–40 µM) is narrower than those for ArteFill (30–50 µM). However, at this time, the medical significance of this difference is not clear.

In 2006, 5 years following the successful pivotal study using Artecoll, the FDA approved ArteFill. In 2006, Aphrodite Gold was launched in Europe. In 2007, Artecoll was relaunched as ArteSense in Canada, with a new syringe to improve injectability. Until 2007, prior to the approval of ArteFill in the United States, European Medical Contract Manufacturing (aap bio implants group) had been the only manufacturer of the PMMA filler (Table 5). PMMA is the permanent particle-based dermal filler that has been on the market the longest.

PARTICLE-BASED FILLER CONTROVERSY

There has been speculation and controversy about the safety of permanent and semipermanent particle-based fillers. It has been suggested that particle-based fillers carry risks such as clumping, migration from the injection site, necrosis, and granuloma.[4] Unsatisfactory correction is also a significant risk because the particles may be permanent or at least long lasting. Although particle-based fillers may seem somewhat similar in their composition (eg, hydroxyethylmethacrylate and ethylmethacrylate

TABLE 5

Presentation and Pricing of Polymethylmethacrylate

Product	Packaging	Price/Box	Price/mL
ArteSense	4×0.7 mL	$1500 Can$ (US $1490) (2.8 mL)	$536 Can$
ArteFill	3×0.8 mL + 2×0.4 mL	$2400 (3.2 mL)	$750

[Dermalive], PMMA [Artecoll]), their respective efficacy and safety profiles should never be assumed to be identical. Dermalive has one of the highest rates of granuloma, whereas Artecoll has one of the lowest rates.[2] The nature of the materials involved and the morphology of the particles are important factors that will directly impact the biocompatibility of particle-based fillers. Animal experiments have demonstrated that the absolute round shape, smooth surface, and size of PMMA microspheres are important to biocompatibility in the skin.[5] This is a characteristic of PMMA in the fillers discussed. Hydroxyethylmethacrylate and ethylmethacrylate is different; its particles are irregularly shaped.[6]

PATIENT PROFILE

Is there an ideal patient profile for the PMMA filler? Aside from the contraindications provided by the manufacturers (eg, known allergy to collagen, lidocaine, or both; known immune or autoimmune diseases; susceptibility to keloids), the authors believe that, generally, if the patient is not afflicted by any condition that interferes with proper healing and normal scar tissue formation, he or she may potentially be a good candidate. Secondary conditions should also be assessed. A thin skin may lead to visible bumps or an implant that is visible through the skin. Age is also a consideration. Often, the real medical profile of a patient is not known until the patient reaches a certain age. Very young patients will go through several physical changes during their lives. Consequently, they may not be ideal candidates. A minority of the panel treats only patients 30 years of age or older with PMMA. Since PMMA is permanent, emotionally unstable patients may pose a risk, as their decisions or expectations may be volatile or unrealistic. On the other hand, because of its permanency, PMMA may be ideal for patients who seek long-lasting results with a minimum number of visits, unlike the temporary fillers, which require that patients have injections regularly to maintain aesthetically acceptable results. Whereas for some patients, multiple visits, repetitive injections, and cost are not concerns, they are for others. A recent article discussing patient retention following botulinum toxin type A injections highlighted that retention could be as low as 44% and was negatively affected by the cost of the procedure and the necessity of scheduling repeat treatments.[7] The panel believes that PMMA may be an ideal alternative for these patients who may suffer from injection and credit card fatigue.

INDICATIONS

The indications that may be treated with PMMA are numerous. Nasolabial folds, mentolabial folds, deep wrinkles, traumatic scars, dermal and subcutaneous skin conditions and imperfections, lip augmentation (particularly suited for post–cleft lip surgery), small facial defects, and acne scars are examples of applications. Some of these indications are easier and more appropriate for beginning injectors, whereas others require a perfect control of the syringe, an excellent knowledge of the anatomy, and a precise technique to place the implant in the desired plane. There is consensus among the group that the indications for which PMMA particle-based fillers are best suited are nasolabial folds, vermilion borders, vertical lip lines, distensible acne scars, and prejowl sulcus. Indications such as tear troughs and lip augmentation (injection along the wet-dry border) should be left to highly experienced PMMA injectors. The nasolabial folds are the ideal indication for PMMA first-time injectors. PMMA should not be the first option for new injectors, who should begin instead with temporary fillers. With PMMA, successful aesthetic results are obtained through progressive augmentation rather than a single volumizing application.

AVOIDING SIDE EFFECTS

Just like any other medical procedure, procedures using particle-based dermal fillers must be performed by qualified physicians. The qualified injector will select the appropriate patients and indications and will inject in the desired and appropriate plane using an ideal technique.

There is no perfect product; they all have the potential for complications.[8] Complications will vary in degree of seriousness as well as the extent to which they can be avoided. As discussed earlier, not only is the biocompatibility of the material important, but the experience and the technique of the injector are as well. The ideal PMMA injector will accurately assess the patient and the treatable indications and consistently inject in the desired plane.

There was consensus among the panel that the side effects of most concern are ridges, visible implants, nodules, and granulomas. The first 3 are directly and solely related to the injector. They are the results of a mispositioning of the implant, overinjection of material in the plane, or both. Hence, there is no doubt that injection technique impacts side effects. The cause of granulomas is less clear, and their occurrence is a potential outcome with all injectable fillers. Although they may be triggered by biological factors such as systemic infection, we believe that they may, in part, also be related to the injector's technique. Although there are no data to support this statement, it was concluded at the summit that the most experienced injectors see substantially fewer cases of granulomas. Among this group, 18,472 syringes were injected, and only 9 patients experienced granulomas, for a rate of 0.049% (calculation based on cases per syringe).

Generally speaking, tunneling (or line threading) is the method recommended for most indications. Following this technique and using different patterns such as fanning or crosshatching (to name a few), the initial implant is deposited slowly (≈0.3 cc/min) and deeply intradermally (ie, into the reticular dermis just above the junction between the dermis and the subcutaneous fat). A trained injector will know exactly where that plane is. The rate of injection is also critical to minimize bruising and pain and to ensure accurate product placement. The second implant should be placed just above the first one. Note that for some applications (eg, lips), it may be pertinent to pretreat with botulinum toxin type A to minimize facial movement in the area and enhance the aesthetic results.

The microdroplet technique is used in the case of puncturelike defects, such as ice-pick acne scars. As mentioned earlier, successful results come with technique and progressive building of the augmentation, avoiding overcorrection. The expert panel is not aware of any reasons related to toxicity of the material justifying a limitation in the amount of product used.

To avoid inaccurate assessment of the correction to be done, the patient should be sitting upright so that the skin is in its normal position. Since PMMA is a bioactive implant (ie, it is a host-tissue growth stimulator), it is necessary to wait approximately 3 months between injection sessions to adequately monitor the progression of the correction and to achieve superior results.

Based on the experience of the group, areas of thin skin or areas requiring a placement of the implant in the upper dermis, such as crow's-feet, superficial lines, or neck lines, should be avoided. Although there is no scientific evidence indicating that this may be a source of complications, for medicolegal reasons, this panel does not recommend building on top of a preexisting permanent or semipermanent filler of a different brand or composition. On the other hand, no objection was voiced to placing temporary fillers such as hyaluronic acid on top of a preexisting PMMA implant, provided that the preexisting implant has been in place for at least 3 months.

To reduce the risk of a blocked needle, prime the syringe to extrude a tiny amount of material prior to inserting the needle. Although bending the needle has no influence on the incidence of side effects, using the needle with the bevel facing up may help navigate the plane of injection, thus improving its accuracy. Needle size has no impact on side effects but will maximize comfort and minimize needle trauma. For the vermilion border and glabella, a 30-gauge needle is preferred.

After the injection, the area should be gently palpated, not massaged, to feel for the presence of any lumps. If a lump is felt, it should be lightly flattened or sculpted to avoid future bumps. It is necessary to instruct the patient to minimize

TABLE 6

Options for Treatment of Granulomas[2,9-11]

Condition	Treatment
Initially and as response begins	Intralesional triamcinolone 20 mg/mL: 5-fluorouracil 50 mg/mL* Intralesional triamcinolone 10 mg/mL: 5-fluorouracil 50 mg/mL*
In areas where there is already lipoatrophy or dermal atrophy	Intralesional triamcinolone 5 mg/mL: 5-fluorouracil 50 mg/mL*
If there is dermal atrophy	Intralesional triamcinolone 2.5 mg/mL: 5-fluorouracil 50 mg/mL*
If there is visible atrophy	Intralesional 5-fluorouracil 50 mg/mL, <1 cc total
If area is very inflamed without risk of atrophy	Intralesional triamcinolone 20 mg/mL
Others	Intralesional saline with or without lidocaine to soften granuloma with simultaneous subscision using 27-gauge or 30-gauge needle Intralesional betamethasone 5–7 mg Larger inflammatory granulomas have shown some favorable response to 1064-nm long-pulsed dye laser Flash lamp pulsed dye laser 595 nm or intense pulsed light combined with betamethasone and 5-fluorouracil

*Triamcinolone X mg/mL with 5-fluorouracil 50 mg/mL in a ratio of 1:1; patient should never receive more than 1 mL 5-fluorouracil 50 mg/mL.

facial mimicry for 72 hours following injection to avoid implant displacement. The use of botulinum toxin type A or an adhesive bandage or tape may be a useful tool to stop any movement and to remind the patient not to move the area previously injected. For obvious reasons, dental work is contraindicated for at least 2 weeks following the implantation of PMMA. Patients should be informed that in some cases of lip injection, it may be normal to feel the implant.

Although not mandatory in all countries because of the low level of allergenicity of the atelocollagen used in the PMMA implant, it is wise to perform an allergy test a few weeks prior to beginning the treatment.

TREATING SIDE EFFECTS

It is important to distinguish between a nodule and a granuloma. The former is a single, well-confined mass effect of agglutination of implant material (eg, PMMA) and appears immediately within the first month. The nodule does not grow.[2] The latter is the body's response to a foreign substance and consists of a small nodular delimited aggregation of inflammatory cells, including lymphocytes, macrophages, and giant cells. Granuloma formation is a rare complication that occurs normally at least 6 months to years after injection and often simultaneously at all implantation sites. Granulomas grow fast and react well to intralesional steroid injections.[2] Untreated, the granuloma can reach the size of a pea but may resolve spontaneously after some time. The PMMA particle-based filler has one of the lowest rates of foreign body granuloma.[2]

The authors feel that there is tremendous confusion as to what constitutes a granulomatous reaction. Very often a nodule is mistaken for a granuloma and should be treated differently. A careful histologic examination is necessary. It is crucial to be able to clinically and histologically differentiate nodules from granulomas, since corticosteroids are effective in cellular proliferations but not in nodules of clumped particles or microspheres.[2] Furthermore, the presence of foreign body cells does not mean a biopsy specimen is pathologic.[8] The nodule can be broken down with a large-gauge (eg, 18-gauge) needle and dispersed or removed with a small biopsy punch from inside the mouth. The treatment modalities for granulomas often include corticosteroids (Table 6).[2,9-11] This panel does not favor massive doses of intralesional triamcinolone or topical corticosteroids.

USING PMMA IN CONJUNCTION WITH OTHER PROCEDURES

For the correction of certain defects, the use of PMMA with other collagen-stimulating procedures may be considered. However, the majority of the panel felt that a waiting period of 3 months should be observed for the implant to integrate properly prior to performing other procedures (eg, lasers, Thermage).

SUMMARY

Suspended PMMA, as found in permanent injectable fillers, has been proven to provide long-lasting results for several indications. This translates into high patient satisfaction, as evidenced by 84% of the respondents to the Artecoll survey. As with any medical procedure, side effects may be expected but can be treated. PMMA, through its long history, has maintained an excellent safety record, and side effects can be kept to a minimum with careful selection of candidates, indications, and appropriate injection technique.[5] Contrary to temporary fillers, which may be more forgiving because of their temporary nature, PMMA requires a higher level of skill and experience. The authors believe that extensive training and use are imperative to achieve a rewarding outcome with minimal side effects.

REFERENCES

1. Sengelmann RD, Tull S. Dermal fillers. www.emedicine.com/derm/topic515.htm. February 7, 2006. Accessed January 23, 2008.
2. Lemperle G, Rullan PP, Gauthier-Hazan N. Avoiding and treating dermal filler complications. *Plast Reconstr Surg.* 2006;118(3 suppl):92S-107S.
3. Hamilton D. A pilot study of the first patients treated in United States with Artecoll implantation for the aging face. *Cosmet Dermatol.* 2001;14(9):47-51.
4. Dermal filler FAQs. http://www.injectablesafety.org/dermalfillers/df_faq.php. Accessed February 5, 2008.
5. Cohen SR, Berner CF, Busso M, et al. ArteFill: a long-lasting injectable wrinkle filler material—summary of the U.S. Food and Drug Administration trials and a progress report on 4- to 5-year outcomes. *Plast Reconstr Surg.* 2006;118(3 suppl):64S-76S.
6. Dermatech. Our technology: our solution. http://www.dermatech.fr/en/rubrique.php3?id_rubrique=4&id_article=18. Accessed January 23, 2008.
7. White L, Tanzi EL, Alster TS. Improving patient retention after botulinum toxin type A treatment. *Dermatol Surg.* 2006;32:212-215.
8. Nicolau PJ. Long-lasting and permanent fillers: biomaterial influence over host tissue response. *Plast Reconstr Surg.* 2007;119:2271-2286.
9. Gelfer A, Carruthers A, Carruthers J, et al. The natural history of polymethylmethacrylate microspheres granulomas. *Dermatol Surg.* 2007;33:614-620.
10. Cheung ST, Lanigan SW. Granuloma faciale treated with the pulsed-dye laser: a case series. *Clin Exp Dermatol.* 2005;30:373-375.
11. Manuskiatti W, Wanitphakdeedecha R, Fitzpatrick RE. Effect of pulse width of a 595-nm flashlamp-pumped pulsed dye laser on the treatment response of keloidal and hypertrophic sternotomy scars. *Dermatol Surg.* 2007;33:152-161. ■