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Article in *Journal of the American Academy of Dermatology* · April 2014

DOI: 10.1016/j.jaad.2014.02.034 · Source: PubMed

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A double-blind, randomized, multicenter, controlled trial of suspended polymethylmethacrylate microspheres for the correction of atrophic facial acne scars

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Background: Acne scarring remains a stubborn clinical problem. Few treatments have been shown to be definitely effective for this problem. Polymethylmethacrylate (PMMA) microspheres in collagen (ArteFill, Suneva Medical Inc, Santa Barbara, CA) have shown long-term benefit for nasolabial fold treatment. A pilot study has shown benefit for PMMA-collagen in atrophic acne scarring.

Objective: We sought to demonstrate the safety and effectiveness of PMMA-collagen for acne scarring in a controlled, blinded trial.

Methods: Subjects with at least 4 moderate to severe rolling, atrophic scars randomly received PMMA-collagen or saline injections. Subjects underwent up to 2 injection sessions and were followed up for 6 months. Efficacy was assessed using a validated rating scale for each scar.

Results: In all, 147 subjects underwent injections. Success was achieved by 64% of those treated with PMMA-collagen compared with 33% of control subjects ($P = .0005$). The treatment showed excellent safety with generally mild, reversible adverse events. No significant differences in efficacy or safety were noted between genders, for darker skin types, or in older age groups.

Limitations: Subjects were followed up for only 6 months.

Conclusion: PMMA-collagen demonstrates substantial effectiveness in the treatment of atrophic acne scars of the face while maintaining an excellent safety profile. Further follow-up should be undertaken to demonstrate longer-term benefit and safety. (J Am Acad Dermatol <http://dx.doi.org/10.1016/j.jaad.2014.02.034>.)

Key words: acne; acne scars; collagen; dermal filler; microspheres; polymethylmethacrylate.

Acne vulgaris affects approximately 40 million people in the United States and it is estimated that up to 90% of adolescents will have acne at some time.^{1,2} The incidence

of scarring from acne has been estimated to range from 1% to 12%.^{3,4} Although somewhat difficult to classify, acne scars have been generally categorized into 3 types: icepick, boxcar, or rolling

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Supported by Suneva Medical Inc.

Conflicts of interest: None declared.

Accepted for publication February 24, 2014.

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Published online April 8, 2014.

0190-9622/\$36.00

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<http://dx.doi.org/10.1016/j.jaad.2014.02.034>

scars.^{5,6} Most patients have a mix of several types of scars.

Treatments for acne scars are dependent on the type of scar. Icepick scars are generally amenable to punch excision.⁷ Boxcar and rolling scars are broader and require other therapy such as subcision, resurfacing, or dermal filling. Although many therapeutic options are published, most are case reports, personal experiences, or small series from a single center. In the past, bovine collagen (Zyplast, Collagen Corporation, Palo Alto, CA) had been approved by the US Food and Drug Administration (FDA) for the treatment of acne scars but was subsequently removed from the US market. No other filler carries US FDA approval for treatment of acne scars. Several 510(k) medical devices are US FDA cleared for use in acne scarring but such clearance requires only modest evidence of clinical efficacy and safety.⁸

Polymethylmethacrylate (PMMA) suspended in bovine collagen (ArteFill, Suneva Medical Inc, Santa Barbara, CA) has been US FDA approved for the treatment of nasolabial folds since 2006. It is similar to other filling materials in its ability to augment soft-tissue defects and is generally considered long lasting. A pilot trial in atrophic acne scars showed considerable benefit.⁹ To demonstrate the efficacy and safety of PMMA-collagen for the treatment of atrophic acne scars for the purposes of US FDA registration, a multicenter clinical trial was undertaken.

METHODS

This study was a double-blind, randomized controlled trial and conducted at 10 investigative centers across the United States with expertise in dermatology and plastic surgery ([Cintrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01559922) identifier: NCT01559922). Before screening, subjects underwent an informed consent process and signed an institutional review board–approved informed consent form. The study was conducted in accordance with Good Clinical Practices and the principles that have their origins in the Declaration of Helsinki (revised Seoul, Korea, 2008).

Potential subjects with acne scars were selected from the investigators practices and solicited from advertisements. To be included, subjects must have met the inclusion and exclusion criteria shown in [Fig 1](#). Each study center incorporated a treating investigator

who performed the injections and a blinded investigator who performed subject evaluations only without knowledge of the treatment assignment.

Before treatment, all of a subject's facial acne scars were evaluated and each scar that met the inclusion and exclusion criteria and was within the treatment area was mapped and photographed. Skin testing

consistent with the labeling for PMMA-collagen was performed before treatments were administered. Subjects were randomized to receive either PMMA-collagen or saline injections in a 2:1 fashion, respectively, using a randomization system that controlled for gender and Fitzpatrick skin type. Treatment centers had no access to randomization data. Four weeks after their first injections, subjects were

re-evaluated and any scars that the blinded evaluator thought were not sufficiently corrected underwent a touch-up injection. Subjects were evaluated at 2 weeks, and 1, 3, and 6 months after their last injections.

Implant material or a saline control was placed at the reticular dermal level or dermal subcutaneous junction. Investigators were encouraged to perform injections using the retrograde linear threading technique but could also perform serial puncture based on actual scar response. For the linear threading, investigators made several passes in one direction and then several additional passes 90 degrees to the original direction. Because of the long-term nature of PMMA-collagen, overcorrection was specifically avoided and investigators were asked to rely on the touch-up injections to achieve the best overall appearance. Commercial PMMA-collagen and needles included with the packaging were used for the injections. Control injections were performed with preservative-free saline in a similar manner.

Scar severity was assessed using a proprietary Acne Scar Rating Scale (ASRS). This 4-point scale (1 = minimal, 2 = mild, 3 = moderate, and 4 = severe) was developed and validated specifically for this study (data on file). This is a photonumeric scale that yields a static score in which each scar receives an individual grade at a designated time point. In addition, assessment was conducted using Physician and Subject Global Aesthetic Improvement Scales ([Fig 2](#)). Lastly, subjects were asked to assess their level of satisfaction of scar correction using the scale

CAPSULE SUMMARY

- Acne scarring remains a common and difficult-to-treat condition.
- This study demonstrates safety, efficacy, and tolerability of polymethylmethacrylate microspheres in collagen for the treatment of acne scarring.
- Physicians may now offer a minimally invasive treatment to their patients with acne scarring.

Abbreviations used:

AE:	adverse event
ASRS:	Acne Scar Rating Scale
FDA:	Food and Drug Administration
PMMA:	polymethylmethacrylate

shown in Fig 3. For each of these assessments, raters were instructed to direct their attention only to treated scars and use the pretreatment photographs for reference.

To ensure uniformity of grading, investigators performed all evaluations with the subject positioned in a stereotactic jig with consistent tangential lighting. Both the treating and blinded evaluators performed their evaluations in this manner. This same jig was used to take standardized photographs.

Safety was evaluated through adverse event (AE) reports at each follow-up visit. Specific attention was paid to reports of hyperpigmentation, hypopigmentation, hypertrophic scarring, or inflammatory responses such as granulomata. In addition, subjects were provided diaries containing prompts to record their experiences for up to 14 days after injections.

Data analysis

The primary analysis population included all subjects screened, randomized, and who received at least 1 injection of study product or control. Subjects with missing data were imputed based on previous results and baseline ASRS as described by Rubin.¹⁰ Treatment success was defined as any subject for whom 50% or more of treated scars improved by at least 2 points using the ASRS as performed by the blinded investigator at month 6. Safety data were tabulated and analyzed for any differences between the populations using Fisher's exact test.

RESULTS

A total of 199 subjects were screened, 175 were randomized, and 147 received at least 1 injection and were included in the primary analysis. The disposition of subjects is shown in Fig 4. The average age was 44 years and 39% were male. Darker-skinned races were well represented with more than 20% of all participants reporting Fitzpatrick skin types V and VI. No statistical differences between the PMMA-collagen and control population demographics were noted.

A total of 1288 scars were treated, 863 in the PMMA-collagen group and 425 in the control group. Subjects in the PMMA-collagen group had an average of 8.9 (range 4-23) scars treated versus 8.5

(range 4-17) for subjects receiving the saline control. Each scar received, on average, 0.11 mL of PMMA-collagen or 0.18 mL of saline. The maximum amount of PMMA-collagen or saline injected into any scar over 2 sessions was 0.42 and 0.80 mL, respectively. No subject received more than 5.8 mL of PMMA-collagen or 8.0 mL of saline in total. The proportion of subjects receiving touch-up injections was similar: 82.5% for PMMA-collagen subjects and 80% for subjects receiving the saline control.

Efficacy

At the predefined end point of 6 months after injections, 64% of PMMA-collagen-treated subjects met the criteria for success (a 2-point improvement in the ASRS score for at least 50% of scars) compared with 33% for the control group ($P = .0005$). PMMA-collagen showed a statistically significant benefit as early as 2 weeks after the second treatment and continued through 6 months as shown in Fig 5. Examples of subjects' clinical results are shown in Fig 6. The overall proportion of scars that improved by at least 2 points was 50% for PMMA-collagen and 21% for the control. With a relaxed threshold for success of a 1-point improvement in the ASRS score, a full 91% of PMMA-collagen-treated scars showed improvement compared with 76% for saline-treated scars.

The Physician Global Aesthetic Improvement Scale score demonstrated an even greater response with 84% of PMMA-collagen subjects rated as improved compared with 54% for the control group ($P = .0003$). Like the ASRS assessments, the response after treatment was prompt. The Physician Global Aesthetic Improvement Scale scores over time are shown in Fig 7, A. The subjects' impressions of the treatment compared favorably with those of the investigators as shown by their Subject Global Aesthetic Improvement Scale scores in Fig 7, B. Subjects showed a high degree of satisfaction through their scores on the Subject Assessment of Scar Correction. A total of 84% of PMMA-collagen-treated subjects were satisfied or better compared with 52% for the saline control group.

Analyses of correlation between efficacy and other parameters including volume injected and number of injection sessions showed no association. No significant differences in efficacy were seen between male and female, lighter and darker skin types, or subjects older or younger than 45 years.

Safety

A total of 267 injection sessions were performed, 177 with PMMA-collagen and 90 with the control material. A total of 21 AEs in 17 (17%) subjects were

Inclusion:

- 18 years of age or older
- At least 4 moderate or severe, rolling, distensible atrophic acne scars of the cheek
- Willingness to withhold any confounding therapies

Exclusion:

- Pregnancy or breastfeeding
- Prohibited therapies within a time frame which could obscure the results of the study
- Inflammatory skin diseases including acne (> 3 inflammatory lesions per cheek)
- History of granulomatous or connective tissue disease
- Hypertrophic scarring
- Predominance of acne scars other than rolling scars
- Allergy to beef, beef products or any components of the study materials

Fig 1. Inclusion and exclusion criteria.

Rating	Description
5 = Much improved	Marked improvement in appearance from the initial condition, touch-up treatment(s) is not indicated
4 = Improved	Obvious improvement in appearance from the initial condition, but a touch-up or re-treatment is indicated
3 = No change	The appearance is essentially the same as the original condition
2 = Worse	The appearance is worse than the original condition
1 = Much Worse	The appearance is much worse than the original condition

Note - The subject version of the scale does not contain references to touch up treatments

Fig 2. Physician and Subject Global Aesthetic Improvement Scale scores.

reported for the PMMA-collagen group and 19 AEs in 13 (26%) control subjects. The most commonly reported AEs included injection-site pain, injection-site tenderness, swelling, influenza, and nasopharyngitis, occurring in 2% or more of subjects. Five serious AEs were recorded during the study, none of which were related to the study treatment. No significant differences in the AE profile were noted between the treatment groups.

AEs related to treatment were far fewer. In the PMMA-collagen group 6 events were recorded: 2 instances each of injection-site pain and bruising, and 1 each of injection-site swelling and acne. All were mild with all but the acne event lasting 5 days or less; the acne resolved by day 16. In the saline control group, 2 related events were seen: injection-site pain, which was mild in character and lasted 4 days along with lumpiness that was also mild and resolved after 76 days.

Although special attention was directed toward events of hyperpigmentation, hypopigmentation, hypertrophic scarring, and granuloma formation, none of these events were reported. The single case of lumpiness for the control subject appeared directly after an injection session, was managed with no intervention, and resolved spontaneously, thus not categorized as a granuloma.

In addition to conventional AE reporting, the subjects recorded their experiences through the use of diaries. Subjects were asked to report on a list of reactions noted with dermal filler injections: erythema, swelling, bruising, pain,

"How satisfied are you with the appearance of the acne scars which will be/have been treated?"

- 6 = Very Satisfied
- 5 = Satisfied
- 4 = Somewhat Satisfied
- 3 = Somewhat Dissatisfied
- 2 = Dissatisfied
- 1 = Very Dissatisfied

Fig 3. Subject Assessment of Scar Correction.

itching, lumps/bumps, and discoloration. Almost all reports were mild or moderate in severity with an average duration from 2 days for pain and itching up to a maximum of 6 days for discoloration.

DISCUSSION

This study is a rigorous evaluation of the treatment of acne scars with PMMA-collagen. The study used a parallel design with a similar control therapy thus ensuring the contributive value of the implant. A validated, static scale was used to assess the changes in each treated scar. Treatments were carefully randomized and spread across multiple investigative sites with experience in dermatology and plastic surgery. The number of subjects and scars assessed exceeds any other trial in acne scar treatment. To our knowledge, virtually no other assessment of a single therapy for acne scarring has been so thorough.

The efficacy data clearly support the use of PMMA-collagen to improve acne scarring in patients without active acne. With a strict definition of success where half or more of a subject scars improve substantially, almost two thirds of subjects responded. In all, 91% of scars treated with PMMA-collagen showed improvement when assessed by 1 grade or better improvement on the ASRS score. As expected, the response after injection is prompt, with correction noted in a significant percentage of treated subjects as soon as 2 weeks after injections. In addition this response is durable throughout the 6-month follow-up period. Further follow-up is warranted to ensure longer durability or perhaps demonstrate further improvement as has been seen with other uses of PMMA.¹¹

The AE reporting shows a risk profile as good as or better than other dermal filler treatments.¹²⁻¹⁴ This is even more impressive in light of the greater number of injection sites and overall volumes used compared with those used in other pivotal filler studies. Just as important from the patient perspective are those common local reactions captured here via the subject diaries. These data show that patients can expect only mild or moderate redness, and swelling that will typically last less than a week. This should be viewed in comparison with other treatments for acne scarring such as various resurfacing procedures where the

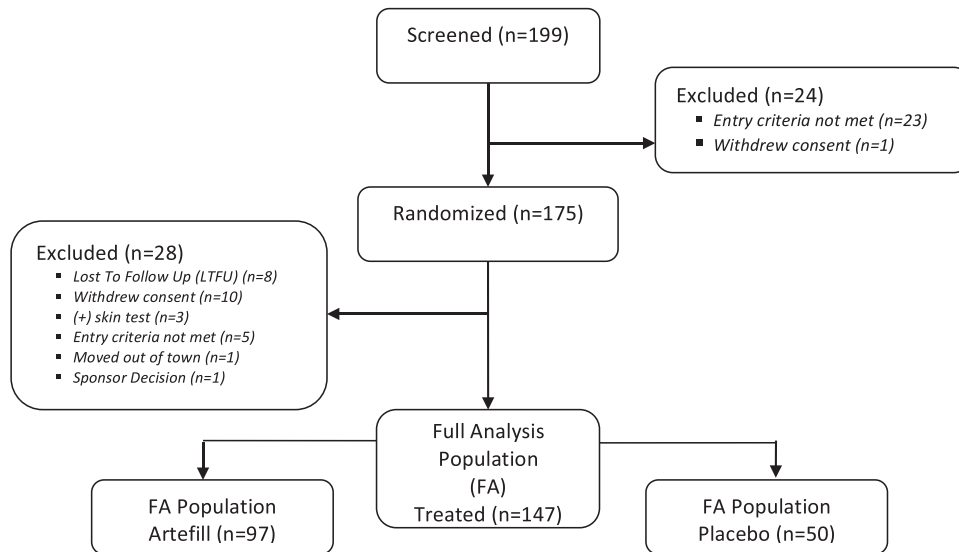


Fig 4. CONSORT diagram.

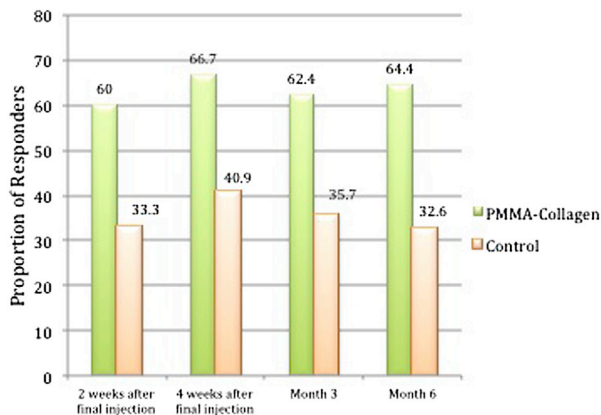


Fig 5. Efficacy as assessed by blinded evaluators using the Acne Scar Rating Scale. Responder defined as subject with 50% or more scars improved by at least two points ($P < .05$ for all time points shown). PMMA, Polymethylmethacrylate.

duration and degree of local reactions can be substantially greater.¹⁵⁻¹⁷

The AEs of special concern, hyperpigmentation and hypopigmentation, along with hypertrophic scarring and late inflammatory reactions attributable to granulomata were not seen. These findings for dyschromia are especially encouraging as darker-skinned patients were abundant in the study population. The complete lack of dyspigmentation combined with excellent efficacy makes PMMA-collagen an excellent treatment option for darker-skinned patients who may be averse to the risks and downtime associated with resurfacing devices.^{18,19}

It is important to recognize that the control treatment in this study is not a placebo. Although

there is no likelihood that any saline solution persists in the area of injection beyond several hours, the act of instillation can have benefit. Subcision is a widely regarded therapy for atrophic acne scars and various needles and techniques have been proffered.²⁰⁻²² Investigators in this study were directed to use a serial threading technique for injection that is similar to the needle movement used for subcision. In addition, it has been demonstrated that biologically inert implants can have stimulatory effects on fibroblasts causing increased secretion of collagen.²³ Thus through both needle action and tissue stretching, the control treatment can effect some improvement in atrophic scars as demonstrated by the rate of efficacy shown here.

The same linear threading technique mimicking subcision was used for both the saline control and the PMMA-collagen material. In our study, the contribution of the implant is clear and persistent. In contrast, other small studies have shown the effect of subcision but no additional benefit from a resorbable implant.^{24,25} Thus using a nonresorbable implant for acne scarring may be the key to superior results and clearly offers benefit over subcision alone.

Any product with long-term persistence merits diligent follow-up. This study presents the early safety and efficacy findings of PMMA-collagen in treating atrophic acne scars. Long-term follow-up of PMMA-collagen in nasolabial fold treatment has continued to show a favorable safety profile²⁶ (data on file). Given the similar characteristics of patients undergoing treatment for nasolabial folds and acne scars, a similar safety profile should be expected with further follow-up.



A

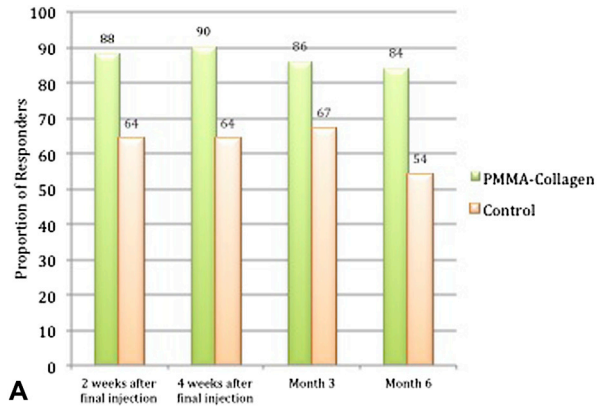


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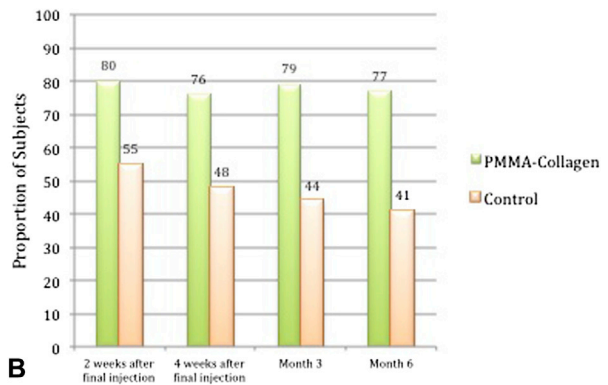


C

Fig 6. **A**, Subject with clinical success ($\geq 50\%$ of scars improved by 2 points on the Acne Scar Rating Scale [ASRS]). Baseline at *left*; 6 months after treatment at *right*. Subject received 2.45 mL of polymethylmethacrylate (PMMA)-collagen to 4 scars in 2 injection sessions. **B**, Subject with clinical success (described above). Subject received 0.46 mL of PMMA-collagen to 6 scars in 2 injection sessions. **C**, Subject with positive results but not achieving clinical success ($< 50\%$ of scars improved by 2 points on ASRS). Subject received 0.78 mL of PMMA-collagen to 6 scars in 2 injection sessions.



A



B

Fig 7. **A**, Efficacy as assessed by blinded Physicians Global Aesthetic Improvement Scale (proportion of subject graded improved or better). **B**, Efficacy as assessed by Subject Global Aesthetic Improvement Scale (proportion of subjects grading themselves as improved or better). ($P < .05$ for all time points shown.)

Conclusion

PMMA-collagen demonstrates substantial effectiveness for the treatment of atrophic acne scars while maintaining an excellent safety profile. Correction occurs quickly and is reliably produced in all races, genders, and ages. The modest local reaction pattern allows patients to undertake this therapy with minimal downtime. Long-term follow-up of PMMA-collagen for nasolabial folds gives reassurance that patients with acne scar are likely to have similar results. Further follow-up is warranted to corroborate the long-term efficacy and continued safety.

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