Modified Poly-L-Lactic Acid Injection Technique

Safety and Efficacy of "Cross-Fanning" in Non-HIV-Related Facial Atrophy

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Abstract: Proper injection of poly-L-lactic acid has a role in avoiding development of subcutaneous papules. We evaluated the safety and efficacy of our injection technique ("cross-fanning") and compared it to 4 previous studies. Forty patients were evaluated for adverse events (bruising, edema, erythema, subcutaneous papules) and satisfaction. Papule incidence was compared with the other studies. The incidence of papules (4/40) was significantly lower than that of VEGA and Chelsea and Westminster ($P = 0.00003$, $P = 0.03$), but not significantly different than APEX002 or Blue Pacific ($P = 0.42$, $P = 0.61$). Bruising (5/40), edema (2/40), papules (4/40), and patient self-satisfaction (80%, $P = 0.0001$) was also documented.

We maintain that cross-fanning has an excellent safety profile and patient satisfaction rate. We also maintain that our modified technique has advantages over the recommended "tunneling cross-hatch" and "depot" technique. Because 38 of 40 patients were HIV-negative, this study also represents the first single-practice series of proper injection of poly-L-lactic acid administration in the immuno-competent patient.

Key Words: poly-L-lactic acid, sculptra, injection technique, subcutaneous papules, granuloma, lipoatrophy, cross-tunneling, cross-fanning, HIV

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Poly-L-lactic acid (Sculptra, Dermik Laboratories, Berwyn, PA) is an injectable product to correct deficiencies associated with lipoatrophy. Currently, poly-L-lactic acid (PLLA) is Food and Drug Administration (FDA)-approved for correction of HIV-associated facial lipoatrophy and has also been used off-label for soft-tissue contouring in the non-HIV patient. PLLA induces collagen synthesis for gradual volumetric expansion that lasts for up to 2 years.[1]

The safety and efficacy of PLLA has been well established in 4 clinical studies involving 277 patients in Europe and the United States, demonstrating that the product is well tolerated and without any serious events.[2–6] The most common adverse event was the development of nonpainful subcutaneous papules, with incidence ranging from 6% to 52%. Histiologic evaluation of the papules revealed the presence of histiocytes and multinucleated giant cells, characteristic of foreign body granulomas.[7] Although the papules usually remain nonbothersome, nonvisible, and less than 5 mm in diameter, they can sometimes require additional interventions including steroid injections and surgical removal.[8,9] As a result, there currently exists a degree of skepticism regarding PLLA use among some physicians.[10]

Injection technique may play a critical role in the development of PLLA-related granulomas.[9,11,12] Currently, most injectors used a depot and cross-tunneling injection technique as recommended by the manufacturer. In this study, we proposed a modified injection technique of PLLA and explored the safety and efficacy of the technique; specific modifications include syringe and needle selection and utilization of a "cross-fanning" method of injecting PLLA. Although the main focus of this study is the safety and efficacy of our modified injection technique, this study also represents the first single-practice series of PLLA administration in the immuno-competent patient.

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METHODS

Study Design

This study examines 66 consecutive patients treated with PLLA for volumetric improvement by 2 physicians in a single practice between the years 2005 and 2007, using our modified injection technique, and all had at least 1-year follow-up from the last treatment session. All patients were contacted by telephone by a blinded surveyor. Forty patients were contacted and participated in the telephone survey. Of the 40 participants, 38 were treated in an off-label manner; these off-label uses included 35 for non-HIV facial esthetic volume loss or malposition (lipoatrophy), and 3 patients for treatment of soft-tissue defects in areas other than the face (1 nipple, 1 lower extremity, and 1 earlobe).

The survey focused on patient-reported safety and efficacy (Fig. 1). Adverse events were explored, including bruising, edema, erythema, and subcutaneous papules. Bruising, edema, and erythema were categorically rated as either "none," "mild," "moderate," or "severe;" "moderate" and "severe" ratings were considered positive measures. Papules were categorized as either "absent" or "present;" "present" was subclassified as "palpable & visible" or "palpable." Additionally, participants were asked to rate the cosmetic outcome with their initial expectations (ie, "no change," "less than expected," "expected," "greater than expected"). Patients rating their outcome as either "expected" or "greater than expected" were considered "satisfied," while "no change" and "less than expected" were considered "unsatisfied."

A retrospective chart review was then performed on the 40 respondents, corroborating the self-reported information with the information documented in the medical chart, including indications, amount of product used, and documented adverse events. Subcutaneous papules were defined as lesions smaller than 5 mm in diameter on physical examination.

Statistical Analysis

The papule outcome measure of the study cohort was compared with the papule outcomes reported in the VEGA,[2] Chelsea and Westminster,[3] APEX002,[6] and Blue Pacific[4] studies. Additionally, patient satisfaction was internally compared within the study series. χ^2 analysis was applied in analyzing interstudy papule incidence and intrastudy patient satisfaction with a significance threshold value of $P < 0.05$.

Reconstitution Technique

Each vial of PLLA (367.5 mg) was diluted at least 24 hours before treatment with 4 mL of bacteriostatic water. Immediately before injection, 1 to 2 mL of 1% lidocaine was added and the

solution was gently agitated in a circular motion. Aggressive agitation or shaking was avoided to prevent the formation of foam which may increase the incidence of needle obstruction during injection.

Injection Technique

Patients to be injected were instructed to avoid anticoagulant medications, red wine, aspirin, and NSAIDS for 10 days before injection to minimize the incidence of bruising and hematoma. The areas to be injected were prepped with alcohol and the PLLA solution was injected using 1 mL Leur-lok syringes (Becton, Dickinson and Company; Franklin Lakes, NJ) and a 1 inch 25-gauge needle.

Patient Survery

1. What was your reason(s) for receiving Sculptra® treatment?
2. Have you received any other cosmetic or reconstructive procedures including injections or surgeries? If yes, did you receive it during the Sculptra® treatment period?
3. Did you have any of the following complications following any of the session of Sculptra® injections?
   - Swelling
   - Bruising
   - Redness

   If yes, please rate the severity as mild, moderate, or severe. How long did the complications last?
4. Did you notice any lumps after the treatments? If yes, could you see and/or feel them?
5. Did you notice a cosmetic difference after receiving Sculptra®? If yes, how did your outcome compare to your expectations? [no change, less than expected, expected, greater than expected]
6. Approximately, how long did your results last after last injection?
7. Did you massage the injection sites after each treatment session?
8. What medications were you taking during the Sculptra® treatment period?

FIGURE 1. Telephone survey administered by a blinded observer to assess indication for treatment, relevant medical history, adverse events, patient satisfaction, post-treatment care, and medications. All collected data of each patient was retrospectively cross-referenced with the patients' medical chart.

We used a "cross-fanning" technique (Figs. 2, 3). Each "fan" is comprised of 5 passes (extensions) from a single injection point. We injected 0.1 mL of PLLA in each pass, with a total of 0.5 mL PLLA injected in each fan. Manual massage of the injected area was performed by the injector after completion of each fan. Additional injections using this fanning method were performed in a crossing manner as needed to produce the desired result. The end point of the injection was individualized to the specific needs of the patient. We did not "overfill" the areas. We injected adequate PLLA solution to provide what we felt was the ultimate desired cosmetic outcome after full treatment.

Manual massage was again performed by the injector after completion of the injection to better disperse the product. Ice was applied and the patient was instructed to perform self-massage of the area. We recommend self-massage of the area 3 times a day for 10 days.

RESULTS

Adverse Event Profile

Adverse events explored in this study include bruising, edema, erythema, and subcutaneous papules (Table 1). Patients were asked to rate the incidence of any adverse events as either none, mild, moderate, or severe. Moderate and severe ratings were considered positive outcomes. Of the 40 patients, only 5 (12%) reported bruising and 2 (5%) reported edema. There was no reported erythema of sufficient rating.

Patients were asked to describe any subcutaneous papules as either palpable and visible or just palpable. Four patients (10%) reported the presence of subcutaneous papules, all located in the periorbital region. All 4 patients described these as "palpable only," and none requested any interventional treatment for these papules.

Comparative Papule Incidence

χ^2 analysis was used to compare the incidence of injection-related subcutaneous papules in the present study to previous studies including the VEGA,[2] Chelsea and Westminster,[3] APEX002,[6] and Blue Pacific[4] studies (Table 2). Using a P value of <0.05, the

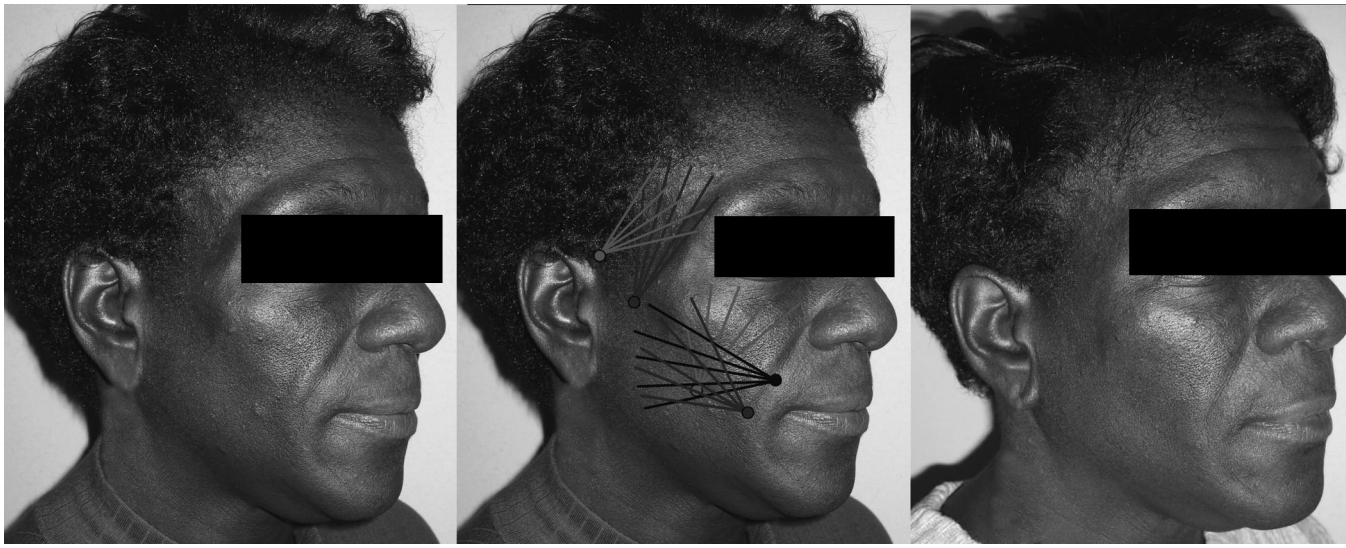

FIGURE 2. "Cross-fanning" injection technique in a patient with moderate facial atrophy. Left, Before treatment demonstrating moderate lipoatrophy of the midface and temporal region; (middle) "Cross-fanning" injection technique; (right) 9-month follow-up after 5 treatment sessions and at total of 10 vials of PLLA. Note the improvement in both the midface and temporal region.

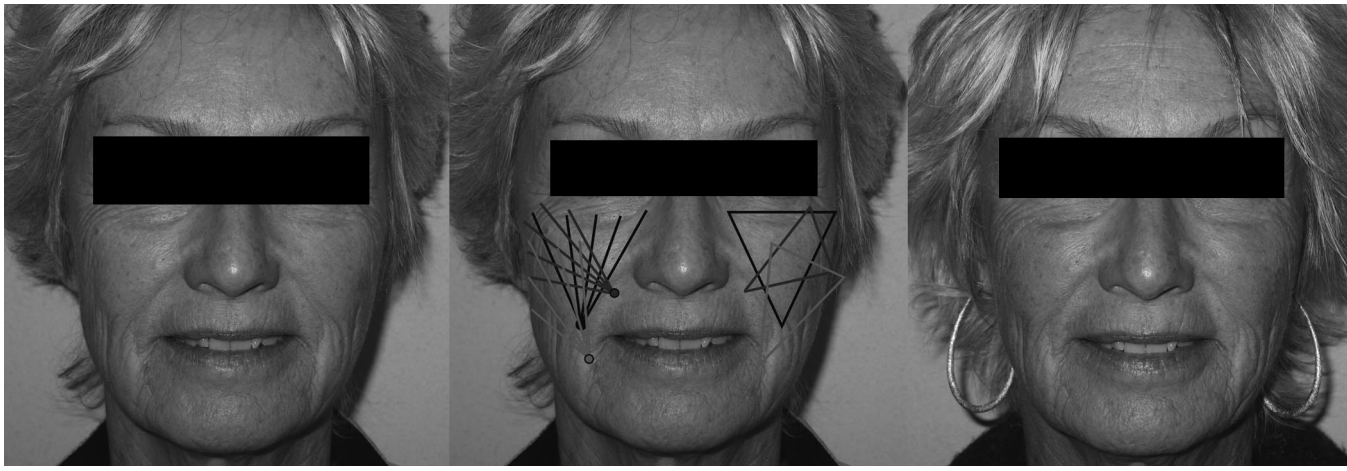

FIGURE 3. "Cross-fanning" injection in a patient with mild facial atrophy. Left, Before treatment demonstrating mild midface volume deficiency commonly seen with aging; (middle) "Cross-fanning" injection technique and "zones of volume replacement;" (right) 9-month follow-up after 3 treatment sessions and a total of 6 vials of PLLA. Note the more youthful appearance of the midface and cheeks.

TABLE 1. Number of Adverse Events Observed in Clinical Studies

Adverse Events	MAPS, n = 40	VEGA Study,[2] n = 50	Chelsea and Westminster Study,[3] n = 30	APEX002 Study,[6] n = 99	Blue Pacific Study,[4] n = 99
Bruising	5 (12%)	3 (6%)	11 (38%)	1 (1%)	30 (30%)
Edema	2 (5%)	2 (4%)	2 (7%)	3 (3%)	17 (17%)
Hematoma	—	14 (28%)	3 (10%)	—	—
Erythema	0	0	3 (10%)	0	3 (3%)
Device-related injection site subcutaneous papule*	4 (10%)	26 (52%)	9 (31%)	6 (6%)	13 (13%)

*Lesions defined as 5 mm or less that typically are non-painful, palpable, non-visible.
MAPS indicates Madison avenue plastic surgery.

TABLE 2. χ^2 Analysis Comparing MAPS Incidence of Subcutaneous Papules to Previous Studies

Study	Subcutaneous Papules	χ^2	*P*
APEX002[6]	6/99	0.66	0.42
Blue Pacific[4]	13/99	0.26	0.61
VEGA[2]	26/50	17.64	0.00003*
Chelsea and Westminster[3]	9/30	4.53	0.03*

*Denotes significant difference between identified study and MAPS in terms of incidence of subcutaneous papules ($P < 0.05$ threshold of significance by χ^2 analysis).
MAPS indicates Madison avenue plastic surgery.

incidence of subcutaneous papules in the present study was found to be significantly lower than the incidence in both the VEGA[2] study ($P = 0.00003$) and the Chelsea and Westminster[3] study ($P = 0.03$). More importantly, however, the incidence of subcutaneous papules in the present study is not significantly different than either the APEX002[6] ($P = 0.42$) or the Blue Pacific[4] ($P = 0.61$) studies.

Patient Satisfaction

Patients were asked to compare the cosmetic outcome with the outcome they initially expected before treatment. Answer choices included no change, less than expected, expected, and greater than expected. Patients choosing expected or greater than expected were considered "satisfied" patients while those choosing less than expected were consider "unsatisfied." Of the 40 patients, 32 (80%) reported a satisfactory rating, while 8 (20%) reported an unsatisfactory rating ($P = 0.0001$). Soft tissue correction can be seen in Figures 4 and 5.

DISCUSSION

PLLA is currently FDA-approved for the treatment of HIV-associated facial lipoatrophy; however, off-label use for the treatment of nonfacial soft tissue defects or treatment in non-HIV patients has been gaining popularity in recent years. In fact, the authors have recently reported the use of PLLA for the correction of a chest wall defect after mastectomy and implant reconstruction.[13] The clinical safety of PLLA in HIV patients has been evaluated by 4 clinical studies: VEGA,[2] Chelsea and Westminster,[3] APEX002,[6] and Blue Pacific.[4] Opponents of the use of PLLA for treatment of soft tissue lipoatrophy point to the high incidence of subcutaneous papules, some of which require surgical excision.[9,10]

Our series shows a 10% incidence (4/40) of nonpalpable subcutaneous papules. We statistically compared our incidence of papules with that in each of the previously mentioned clinical trials. A comparison of the incidence of all our adverse events to the respective incidences in the other studies would require the raw

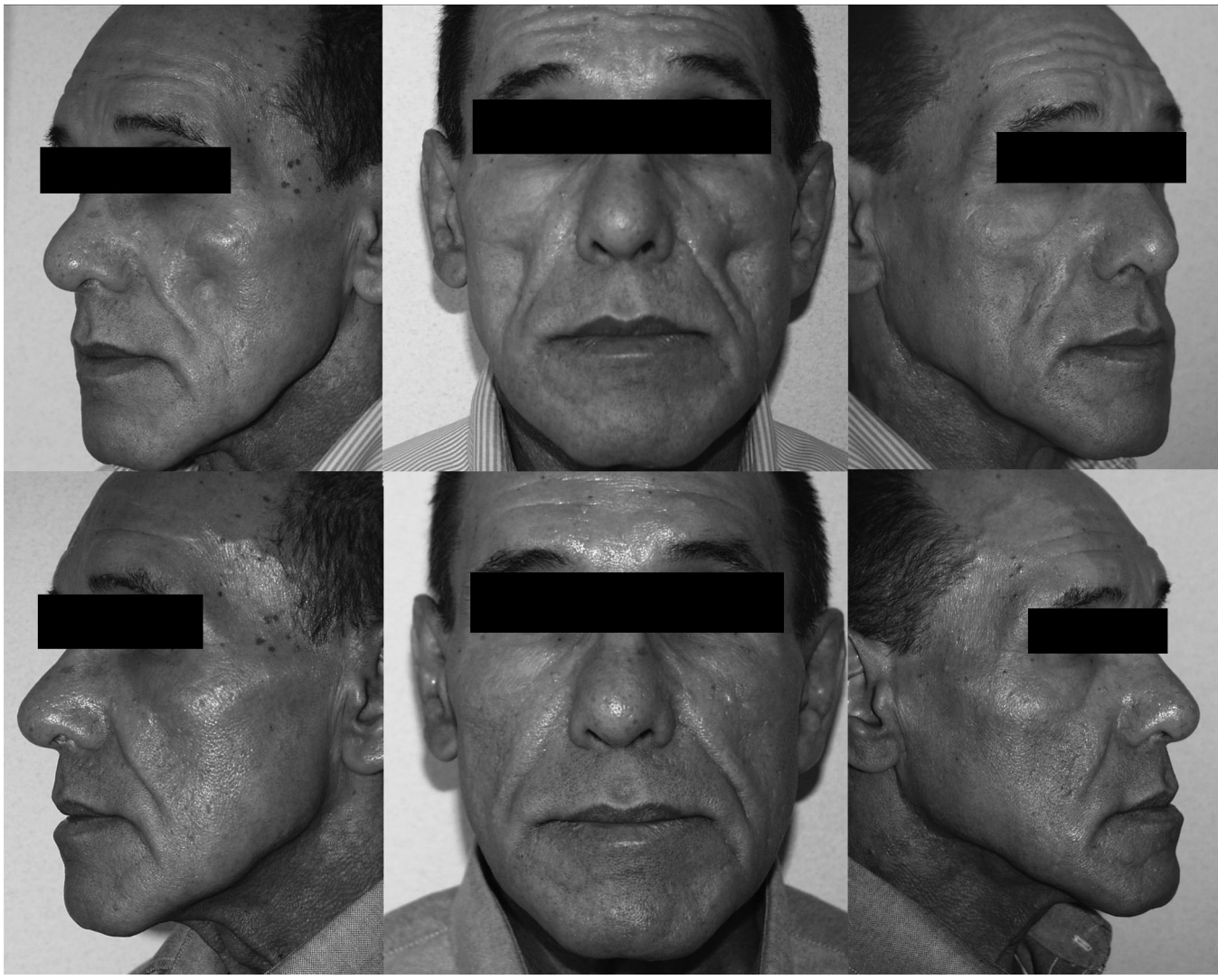

FIGURE 4. Severe facial lipoatrophy. Top row, Before treatment demonstrating severe lipoatrophy of the midface; (bottom row) 9-month follow-up after 2 treatment session and a total of 4 vials of PLLA. Note the improvement in the soft tissue of the midface and cheeks.

patient data from each study to conduct a multivariate analysis. Since we did not have access to such data, we chose to pick one adverse event to conduct a valid comparison. The incidence of subcutaneous papules was chosen because it remains the most significant adverse event related to PLLA usage. The incidence of papules in our patients was significantly less than that in the VEGA[2] and Chelsea and Westminster[3] studies and not significantly different than that in the APEX002[6] and Blue Pacific[4] studies. We considered our incidence to be acceptable, given that all reported papules were nonvisible and only palpable by the physician and the patient. Moreover, none required any subsequent treatments such as steroid injection or surgical excision. Product preparation and injection technique may both play a critical role in maintaining a low incidence of nonvisible papules with PLLA usage.

The manufacture recommends reconstitution of the product "at least 2 hours" before injection, as stated in the product insert. We advocate reconstitution at least 24 hours before use. This allows the product to better dissolve and reduces the incidence of needle clogging during injection. Additionally, a 24-hour reconstitution may minimize the likelihood of PLLA "clusters" being injected that may represent a nidus for papule formation. The manufacturer does acknowledge in the package insert that the reconstituted product is "useable within 72 hours of reconstitution."

The manufacturer also recommends using a "tunneling cross-hatch" injection technique for the mid and lower face, as was done in the aforementioned studies. This method involves placing multiple small amounts of PLLA in a grid-like pattern. Each injection consists of 0.1 to 0.2 mL of PLLA placed into the deep dermal space. We have found that this method is cumbersome to the injector and painful to the patient because it involves large numbers of needle punctures; in fact, approximately 25 to 50 individual injection sites are necessary for each vial of PLLA. This can result in injector fatigue, increased patient discomfort during the injection process, and increased bruising and edema during the recovery. Our cross-fanning technique enables us to spread a thin layer of PLLA over a larger surface area. This thin, uniform layer may allow uniform correction with significantly less skin punctures (10 vs.

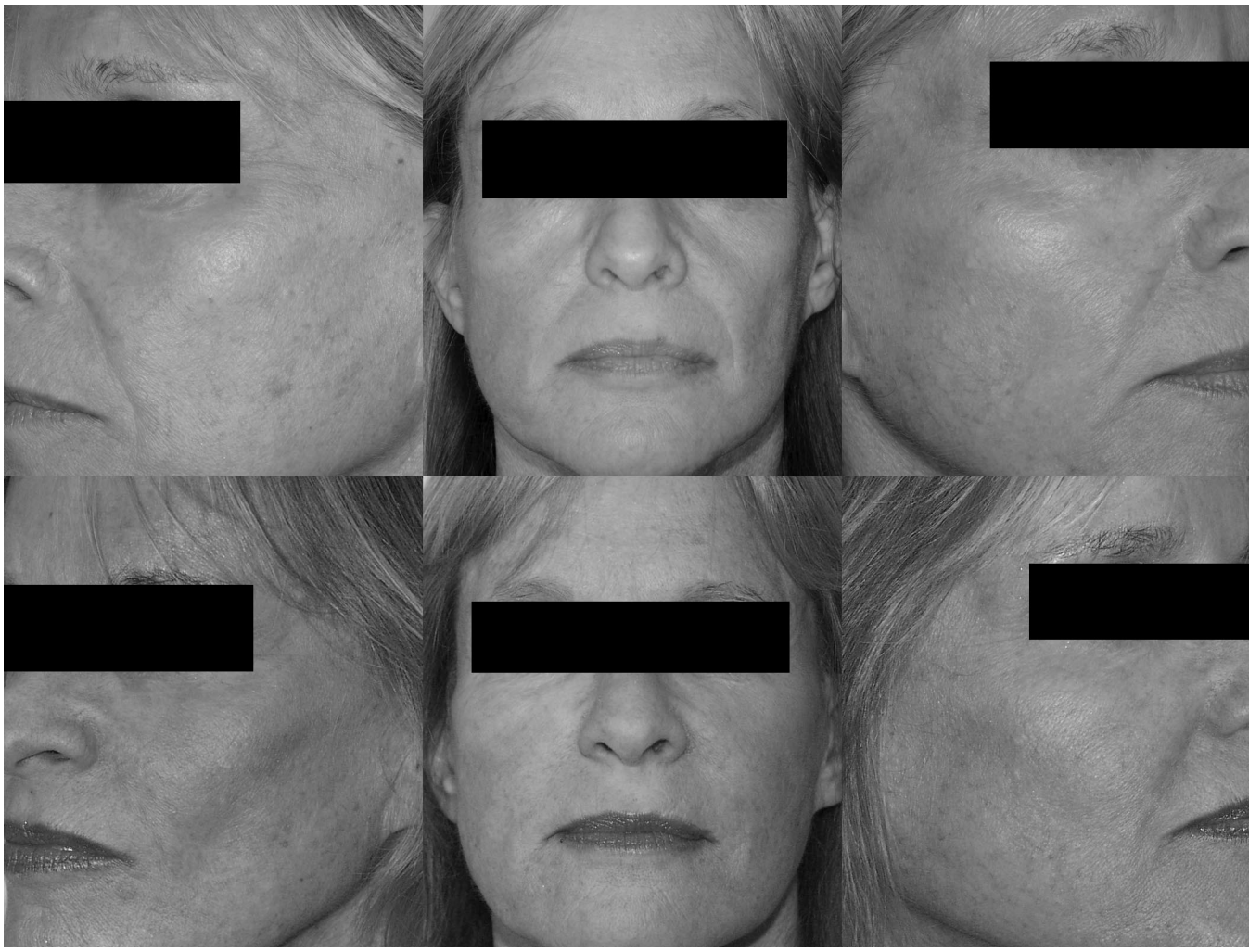

FIGURE 5. Moderate facial lipoatrophy. Top row, Before treatment demonstrating moderate facial lipoatrophy resulting in tear tough deformities; (bottom row) 5-month follow-up after 5 treatment sessions and a total of 6 vials of PLLA. Note the improvement in the midface and infra-orbital region with reduction in visible tear troughs.

25–50 per 5 mL of PLLA). We use a 1-inch needle to span a longer distance and cover a larger surface area.

While the tunneling cross-hatch technique is recommended by the manufacturers for the mid and lower face, they recommend a "depot" technique for correction at the level of the upper zygoma and temples. Multiple injections are made with approximately 0.05 mL PLLA placed under the temporalis muscle on the periosteum per injection. We found that our cross-fanning technique is also appropriate for this upper face region (Fig. 2) for the reasons previously discussed. We also found that a depot technique can be particularly uncomfortable for the patient because the temporalis muscle is being punctured and the periosteum can be very sensitive. This area is also highly vascularized and multiple deep punctures may result in intramuscular bleeding and hematoma. Most importantly, we feel that a depot technique, especially in this thin-skinned area, may increase the incidence of papule formation by placement of small condensed "beads" of PLLA. When we inject in the upper zygoma and temples, we place the product in the space between the superficial and deep parietal fascia, as opposed to a submuscular injection. We find that by injecting in this avascular space, there is reduced bruising and hematoma, and significantly less postprocedural discomfort because the temporalis muscle is not traumatized.

While our incidence of papules was low, we did have 4 of 40 patients report palpable, nonvisible papules in the periorbital region. This is likely due to the extremely thin skin in this anatomic area. It is important to keep injections in the periorbital region deep, below the obicularis occuli muscle, to prevent intramuscular PLLA placement. Placing PLLA into the muscle predisposes to papule formation. Also, if a papule develops below the muscle, it will be well hidden beneath soft tissue. To ensure that PLLA is placed underneath the obicularis occuli muscle, we recommend that injections in the periorbital region are placed 1.5 cm below the orbital rim. Regardless of technique, injection of any material in the periorbital region carries inherent risks and is best reserved for the expert injectors as supported by others' experience with PLLA.[9] Lam et al also warn against injecting PLLA into the lips and nose because the outcomes may be unpredictable in those regions and the esthetic tolerance for error is only a few millimeters.

Like many practitioners,[9,12,14] we recommend patient-based postprocedural massage. While we recommend massaging the area 3 times a day for 10 days, others advocate a "rule of five": 5 times per day, for 5 minutes, for 5 days.[15,16] Regardless of the particular method, it is necessary to stress to the patient the importance of this massaging to help evenly disperse the product. We acknowledge that

patient compliance in this area can be extremely low, and most patients admitted to not massaging as frequently as we recommend (or not massaging at all). This is not surprising and further reinforces the importance of good injection technique because the injector cannot solely rely on postprocedural massaging by the patient to prevent papule formation.

Patient satisfaction was another outcome we explored. Of the 40 patients we interviewed, 32 (80%) reported a satisfactory rating. The 8 unsatisfied patients consisted of 1 reporting no change and 7 reporting less than expected results. The patient who reported no change received 2 treatments with 1 vial of PLLA at each session. This patient failed to return for additional treatments, despite being told during the initial consultation that correcting severe lipoatrophy generally requires 3 to 6 treatment sessions with 1 to 2 vials of product injected per session.[1]

Of the 7 who reported less than expected results, 3 had significant pathologic soft-tissue defects and chose PLLA in an attempt to avoid surgical correction of the defects. The remaining 4 patients described their low satisfaction as cost-benefit imbalance: the cosmetic result did not justify the out-of-pocket cost of off-label PLLA use.

This 20% unsatisfaction rate illustrates the importance of in-depth discussion with potential patients. While many prefer PLLA because it provides a correction with the patients "own tissue," the gradual correction can be seen as a disadvantage to those who want an immediate correction. Potential patients must be given an honest estimation of the amount of product they will require, the cost of these treatments, and how long the process will take. Someone who requires 6 treatment sessions every 4 to 6 weeks must be informed that full correction may not be seen for 8 to 10 months. Additionally, the correction is gradual and progressive, further supporting the importance of preprocedural photography. Oftentimes, the patients do not appreciate the improvement until they are shown "before and after" pictures.

Ultimately, there is no set PLLA-algorithm that can be applied for treating patients with lipoatrophy as outcomes are dependent on an individual's response to the product. However, we do recommend the following guidelines for guiding inexperienced injectors and more importantly, managing patients' expectations regarding the number of treatments and financial obligation. In our experience, it is helpful to divide lipoatrophy into categories of severity: mild, moderate, and severe. Mild cases can expect requiring 2 to 4 treatments, using 1 vial of PLLA at each treatment. Moderate cases can expect to require 3 to 5 treatments, using 2 vials per treatment. Severe cases can expect to require 4 to 6 treatments, using 2 vials per treatment. It should be noted that each treatment should be separated by at least 1 month, and that collagen synthesis in response to the product can take 6 to 8 weeks. Therefore, careful evaluation before later treatment sessions is necessary to avoid "over correction." Less product may be indicated in later treatments as collagen synthesis occurs. Our guiding treatment approach is "evaluate, treat, re-evaluate."

Our study was designed to demonstrate that our injection technique had a safety profile equal to or better than the published literature, but there were a few limitations. There was no randomization or placebo group in our study. However, of the 4 previous studies, only the Chelsea and Westminster study[3] was randomized but also lacked a placebo group. Randomization was not conducted in our study largely because of the retrospective design. Our goal was to review the safety and efficacy of our modified injection technique in as many of our patients as possible, such that randomization was not possible. Additionally, the effectiveness and safety of PLLA as a treatment for facial lipoatrophy has been well established obviating the need for a placebo group. It should also be noted that while our study was retrospective, the other 4 studies were prospective. Retrospective studies naturally have certain limitations, including susceptibility to confounding variables and bias; however, we carefully cross-referenced the patient reported data with a detailed medical history in the medical chart to potentially identify any confounding factors. Nonetheless, continued evaluation of our injection technique will be conducted prospectively.

The comparative safety outcome of this study was the incidence of subcutaneous papules. Our patients served as the experimental group and the patients from previous studies served as the control group. However, the patients in the previous 4 studies were all HIV-positive while most (38/40) of the patients in our study were all immune-competent. Some studies have histologically identified the papules as foreign body granulomas secondary to PLLA.[7–9] Granulomas form in the setting of failure in the acute inflammatory response to a foreign particle and activation of the cell-mediated immune response combined with the recruitment of macrophages.[17] Studies in foreign body reactions among HIV-positive and HIV-negative patients reveal characteristic histologic differences between the 2 patient groups including partial intracellular destruction of foreign material in macrophages; reduced tendency for macrophages to form giant cells; and increased number of mast cells and eosinophils.[18,19] Therefore, the incidence of granuloma formation secondary to PLLA injections should be decreased in the HIV-positive patient compared with the non-HIV patient.

The validity of comparing our immune-competent patients with HIV-positive patients may be questionable only if our results showed a higher incidence of PLLA induced granulomas: the incidence of granulomas may be a function of injection technique, the patient's immune status, or both. However, our results showed comparatively lower to no difference in the incidence of papules. Our results would suggest that our injection technique is responsible for our outcome versus the patients' immune status because our immune-competent patients would be expected to have a higher incidence of papules.

Our similar incidence of papules could also be due to the fact that the HIV-positive patients in the previous studies were all on HAART treatment for at least 3 years. Although immune status is not completely restored, some restoration would help bring the expected incidence of granuloma formation back towards levels similar to immune-competent patients. In fact, foreign body granuloma reactivation has been described in post-HAART treatment HIV-positive patients.[20]

While our goal was to focus primarily on technique, this series also represents the first single-practice series of PLLA administration in the immune-competent patient. Our results suggest that our modified injection technique has maintained a low incidence of papule formation with increased patient comfort in the non-HIV patient despite the increased immune response associated with this patient population. Hopefully, future studies in the non-HIV population will further confirm the safety and efficacy of PLLA use and support FDA approval for this currently "off-label" use of product.

CONCLUSIONS

This series represents a single practice's experience with the use of PLLA for the treatment of soft tissue deficiencies. We propose a modified injection technique: cross-fanning as opposed to "tunneling cross-hatch and depot" techniques. Our results suggest that our cross-fanning injection technique demonstrates safety and efficacy at least equal to the technique used in the previous 4 clinical series while providing greater patient comfort (less needle sticks). We also maintain that this modified tech-

nique may be superior in achieving a smooth and even volumization of soft-tissue deficiencies.

Our experience reinforces the importance of technique in the use of dermal and subdermal fillers. Continued reassessment of technique, and constant modification is necessary to ensure the safe and effective use of this product. Additionally, our study demonstrates PLLA safety and efficacy in the non-HIV patient. This represents an off-label use, but one cannot dismiss the need for a safe and effective soft tissue volumizer in the non-HIV patient, for either cosmetic rejuvenation of the aging face or correction of severe soft tissue deformities throughout the body.

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