Cosmetic Use of Poly-L-Lactic Acid: A Retrospective Study of 130 Patients

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BACKGROUND Poly-L-lactic acid (PLLA) is an effective treatment for patients seeking to correct volume loss due to aging. Although the Food and Drug Administration has approved PLLA for use in people with the human immunodeficiency virus (HIV), it is well-suited for patients seeking cosmetic treatment.

OBJECTIVE To evaluate the efficacy and incidence of adverse events of HIV-negative patients treated with PLLA for volume restoration.

MATERIALS AND METHODS This is a retrospective, single-center study of 130 HIV-negative patients treated with PLLA from 2003 to 2008. Patient satisfaction and incidence of adverse reactions were evaluated.

RESULTS The most common reaction to PLLA treatment was the formation of nodules (8.5%). Almost all of the nodules were palpable; only one was visible. Treatment areas with the highest incidence of post-treatment nodules were the hands (12.5%) and cheeks (7.2%). Overall, patients were satisfied, with 55% having good to excellent correction; 75% of patients with five or more treatments rated their correction as good to excellent. Sixty-eight percent of all patients would repeat the procedure again.

CONCLUSION PLLA is a safe, biodegradable volumizer used to reverse the signs of aging by gradually correcting volume loss. Patients should be aware of possible adverse reactions during the course of treatment. Nodule formation is low, with most patients having good to excellent correction.

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Modern cosmetic technology has given patients the opportunity to reverse the signs of aging, such as wrinkles and loss of volume. Poly-L-lactic acid (PLLA) in the form of Sculptra (Dermik Laboratories, Bridgewater, NJ, a division of Sanofi-Aventis), has been commonly used off-label[1] in the United States to treat patients with loss of volume in areas of the face, chest, and hands. PLLA has been approved since 1999 in Europe as New-Fill under the category of wrinkle filler.[2] The Food and Drug Administration (FDA) approved it in 2004 for use in individuals with human immunodeficiency virus to treat facial volume loss secondary to lipoatrophy. More recently, in August 2009, Sculptra Aesthetic was approved for use in the non-HIV population in the correction of nasolabial folds and other facial wrinkles.

PLLA has been used in various medical applications for more than 3 decades.[3] PLLA is biocompatible—eliciting a negligible immunologic response[2]—but it is a foreign compound. Early murine studies demonstrated a fibroblastic response with increased collagen production after cutaneous PLLA implantation.[4] This synthetic polymer derives from the alpha-hydroxy family and is ideally placed in the dermal–subcutaneous junction or the upper hypodermis to stimulate fibroblastic production of collagen.

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One of the risks of PLLA is subcutaneous nodule formation.[5] The onset of nodule formation from the time of injection can vary. Subcutaneous nodules can form for a variety of reasons: insufficient time during reconstitution of the material, inadequate dilution, overcorrection, superficial injection techniques, inappropriate concentration of PLLA molecules secondary to muscle movement, or allergic or inflammatory host responses.[5] We have rarely seen visible nodule formation and therefore conducted this retrospective evaluation of our nonimmunocompromised patients who had been treated over the last 5 years with PLLA.

METHODS

Written informed consent was obtained from patients participating in retrospective data collection. Study protocol confirmed to current ethical guidelines according to the 1975 Declaration of Helsinki.

Patients

All nonimmunocompromised patients who were treated with PLLA by physicians at our clinic between January 2003 and September 2008 were contacted with regard to efficacy and adverse reactions after their treatment (Table 1). Of the 311 patients treated during that period, 130 (42%) were successfully contacted and asked a series of questions from a standardized questionnaire. One of the authors evaluated all patients in the clinic who had any adverse effects. One hundred eighty-one patients were lost to follow-up; 142 did not return phone calls, 38 had an incorrect address or phone number, and one had died. Information gathered included age; sex; site of injection; dilution; time between treatment and nodule formation; and degree of bruising, discomfort, and satisfaction.

TABLE 1. Patient Survey Pool

Response Category	n *(%)*
Responders	130 (42)
Nonresponders	
Unreturned phone call	142 (46)
Incorrect contact information	38 (12)
Deceased	1 (0)
Total patients	311 (100)

All eligible patients were determined to be good candidates for volume restoration. Female patients were excluded from treatment if pregnant or planning to become pregnant. Patients did not have concurrent autologous fat transfer or hyaluronic acid or collagen filler administration to the areas treated with PLLA. Data collection occurred from June through November 2008.

Material

PLLA, a carbohydrate polymer, is produced through corn dextrose fermentation.[6] PLLA is prepared as micronized, lypophilic polylactic acid with an average particle size of 40 to 63 μm.[7] Each glass vial contains 150 mg of PLLA in a suspension of sodium carboxymethylcellulose and nonpyrogenic mannitol. PLLA was always reconstituted at least overnight and often longer at room temperature in 6 to 11 mL of sterile water. An additional 1 mL of lidocaine 1% with epinephrine 1:100,000 was added before administration. No topical anesthetic, regional nerve block, or application of ice was used before PLLA injections. Agitation using a laboratory vortex was performed immediately before injection starting in April 2007 to decrease the occurrence of needle blockage.

Treatment Administration

All patients were treated in a similar manner regardless of site of PLLA implantation. Three physicians at our facility performed all of the PLLA injections. Immediately before PLLA treatment, the skin was cleansed with an alcohol pad. The recently agitated PLLA was transferred to 1- or 3-mL syringes attached to a 0.5- or 1.5-inch, 25- to 26-gauge needle. PLLA was injected using a fanning technique from one to three injection points into the upper subcutaneous compartment. The exception to this depth of placement was in the temples, tear troughs, and over bone, where PLLA was deposited in a depot fashion above the periosteum. Total product administered varied according to location, but in

general was one vial total per treatment session. In many patients, multiple areas were treated during a single injection session. Treated areas included the cheeks (medial and lateral cheeks, tear trough area), temples, nasolabial folds and marionette lines, chest, hands, and thigh. After injection, the physician vigorously massaged the treated area. Patients were then instructed to follow the "5-5-5" rule: massage treated area for 5 minutes, five times a day, for 5 days. Patients received successive treatments at 4- to 12-week intervals.

RESULTS

Of the 137 patients, the majority were female (86.9%), and the average age of all patients who received treatment was 58.6 (range 38–87; Table 2). Patients received an average of 2.8 treatments (range 1–12). On average, patients received 1.0 vial per treatment, with an average dilution of 8.3 mL per vial.

The great majority of patients (89%) reported at least mild correction of volume loss (Figures 1–4). Overall, 55% of patients experienced good to excellent correction independent of site treated (Table 3). Injections to the temples, hands, and nasolabial folds and marionette lines received the most satisfaction from patients in the level of correction. The hands had one of the greatest incidences of nodule formation (Figure 5) yet the highest level of patient satisfaction, with 63% of patients treated rating correction as good to excellent. Number of treatment sessions was roughly correlated with patient satisfaction. Patients receiving one to two treatment sessions rated their correction as good to excellent 48% of the time. This percentage rose to 50% with three treatment sessions, 67% with four treatment sessions, and 75% with five or more treatment sessions.

TABLE 2. Patient Demographic Data

Sex	n *(%)*	*Average Age*
Male	17 (13.1)	61.6
Female	113 (86.9)	58.1
All patients	130 (100.0)	58.6

Treatment with PLLA had a favorable side-effect profile (Table 4). Only three percent of all surveyed patients experienced significant bruising. Eighty-four percent of patients had no to minimal pain during the procedure. No patients experienced edema, erythema, or infection. The incidence of nodule formation is discussed below.

Table 5 demonstrates that the most common site of injection was in the cheek—an area that included injections to the malar, medial or lateral cheek, and tear trough. One patient received PLLA treatment for a localized atrophic area to the thigh. Excluding this one patient from the PLLA cohort, the chest was the least common site of injection. Of the 130 patients treated, 11 (8.5%) experienced formation of nodules. Separating nodule formation according to area of treatment, eight of 111 patients (7.2%) developed nodules in the cheek area, one of 24 (4.2%) in the temple area, one of 26 (3.9%) in the nasolabial folds and marionette lines, and one of eight (12.5%) in the hands.

The individual characteristics of patients who developed nodules are outlined in Table 6. All patients in this cohort were female. Patients who formed nodules reported their appearance within the first 4 months. All nodules were palpable but non-visible, except for in one patient. The patient with a visible papule was treated unilaterally in the inferior cheek and marionette line for correction of volume loss secondary to Bell's palsy.

The majority of patients who experienced formation of nodules had no bruising (Table 4), and five (45%) said they would repeat the procedure. Only one patient experienced granuloma formation, as confirmed using histopathologic examination (Figure 6). The granuloma formed in the temple area and was treated with subcision and subsequent, definitive surgical excision.

Patient age did not affect nodule formation. Those who developed nodules did not have more treatments than those who did not, the average being 2.7 treat-

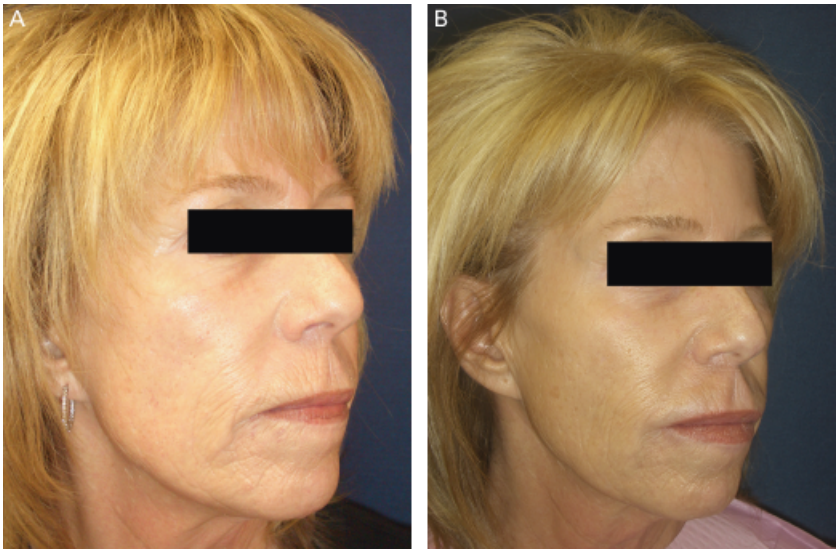

Figure 1. (A) 57-year-old woman before treatment. (B) Same patient after three treatment sessions with poly-L-lactic acid, one vial per treatment, to the cheek area.

ments for those with nodule formation and 2.8 treatments for those with no nodules. The highest number of treatments for those who developed nodules was five, compared with 12 for those who did not.

Average dilution did not seem to predict the formation of nodules. The average dilution for patients who developed nodules was 8.3 mL, compared with 8.1 mL for patients who did not. A higher percentage of nodules formed in areas of the hands and the cheeks. The number of patients receiving treatment to these areas differed markedly; only eight patients had PLLA injections to the hands, whereas 111 patients received treatment to the cheek area.

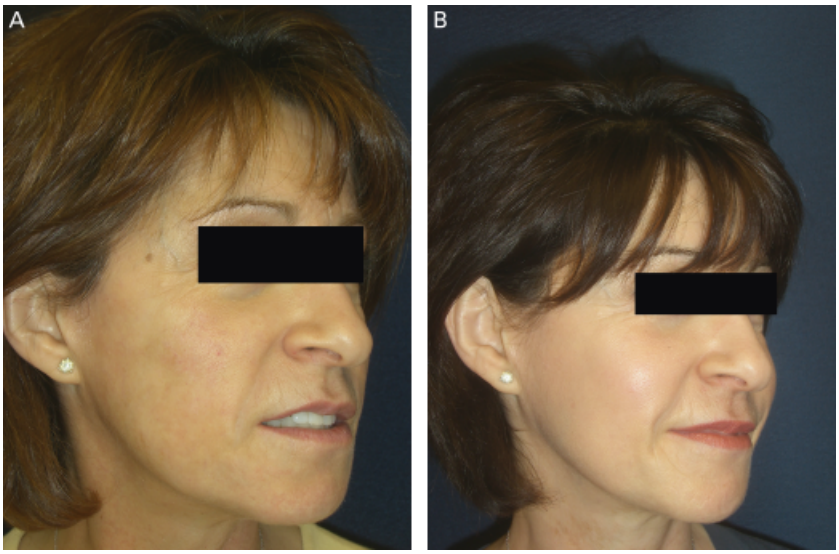

Figure 2. (A) 54-year-old woman before treatment. (B) Same patient after four treatment sessions of poly-L-lactic acid over 12 months, one vial per treatment (8 mL dilution), to the cheek area.

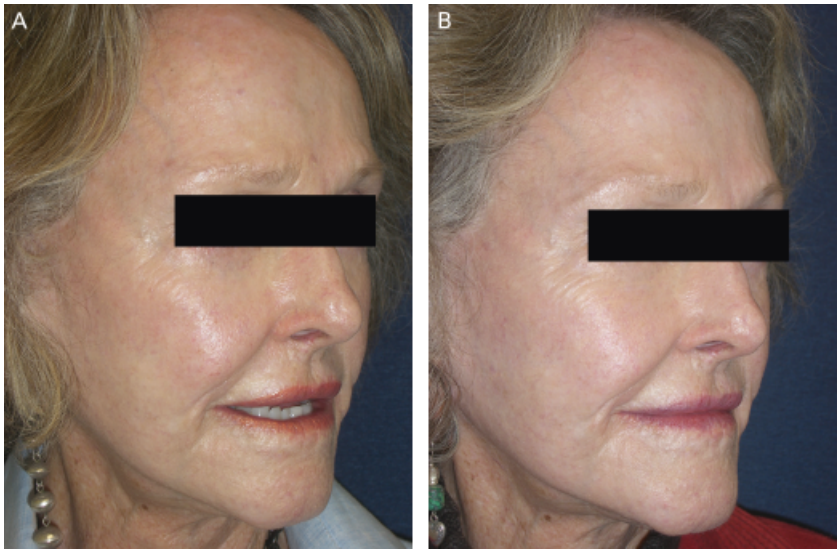

Figure 3. (A) 81-year-old woman before treatment. (B) Same patient after five treatment sessions of poly-L-lactic acid over 22 months, one vial per treatment (8 mL dilution), to the cheek area.

DISCUSSION

PLLA has given physicians and patients a new dimension in facial contouring by revolumizing the aging face through a minimally invasive approach.

The cosmetic experience abroad with PLLA is somewhat different, with nearly 150,000 patients in more than 30 countries treated with NewFill by 2004.[2] One European study has examined PLLA for use as a soft tissue filler,[3] but there are few other reports of PLLA for cosmetic use. The cosmetic application of PLLA was pending at the time of article submission.[8] However, FDA approval was gained in August 2009. Due to the recent FDA approval, the medical literature offers mainly scattered reports of cosmetic, off-label PLLA use exist in the U.S. literature in the HIV-negative population. These include PLLA treatment of a melanoma excision scar,[9] trauma-induced facial atrophy,[10] hand rejuvenation,[11] and acne and varicella scarring.[12]

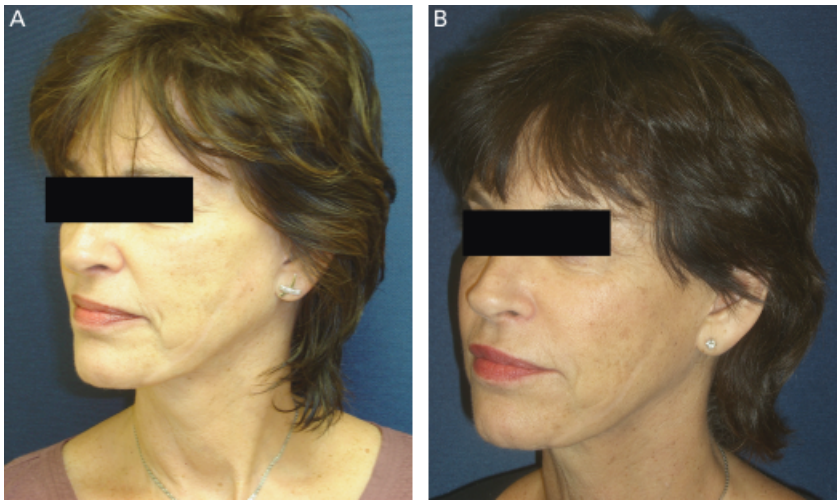

Figure 4. (A) 59-year-old woman before treatment. (B) Same patient after three treatment sessions of poly-L-lactic acid over 19 months, one vial per treatment (8 mL dilution), to the cheek area.

TABLE 3. Number of Treatments and Degree of Correction

		Subjects' Appraisal of Correction of Results, %				
Treatments, n	*Patients,* n	*None*	*Mild*	*Good*	*Excellent*	*Compiled Good + Excellent*
1	37	11	43	30	16	46
2	30	13	37	23	27	50
1 to 2	67	12	40	27	21	48
3	31	3	35	39	23	62
4	16	31	19	25	25	50
≥5	16	0	25	63	13	75
Total	130	11	35	34	21	55

In addition to these case reports, a recent prospective cohort study by Levy and colleagues[13] examined the safety and efficacy of PLLA use in a mixed population of HIV-positive and -negative patients. Despite 18% of the 65 patients being lost to follow-up, the study found a statistically significant improvement of HIV facial lipoatrophy and lipoatrophy of aging. Furthermore, results were durable, lasting up to 3 years with additional PLLA injections. A prior study in 2007 from the same group complements the later findings. Hanke and Redbord[14] found PLLA use in all 65 patients to be safe and efficacious. The 38 HIV-negative patients required approximately half the number of treatments and vials to reach adequate cosmetic correction as the HIV-positive study population.

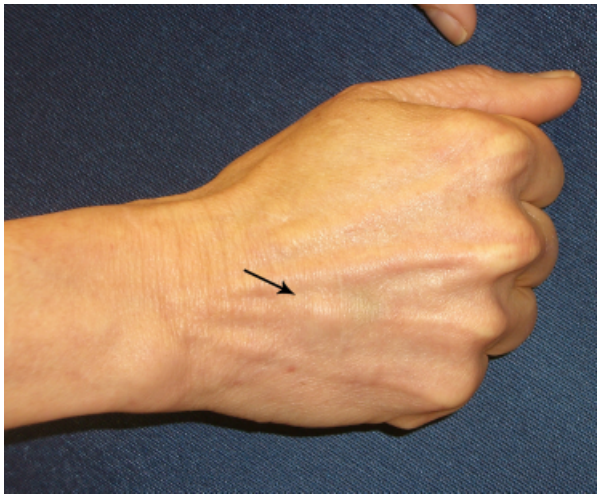

Figure 5. Nodule of the hand 2 months after one poly-L-lactic acid injection using a 12-mL dilution.

Despite extensive use of PLLA for soft tissue augmentation in the United States and abroad, the precise mechanism of action is not completely understood. In accordance with histologic examination and animal studies, it is hypothesized that PLLA elicits a host-dependent immunologic response, resulting in a controlled foreign-body reaction. Fibroblast activity is increased, resulting in neocollagen formation[7] and collagen encapsulation of PLLA particles over the ensuing weeks to months.[15] This "bulking effect," resulting in increased dermal thickness, is not apparent for 2 months.[15] PLLA has a durable response, with continued volume repletion at 2 years. It slowly degrades over time, being

TABLE 4. Patient Evaluation of Treatment

Reaction or /End Point	n *(%)*
Bruising	
None	67 (52)
Mild	45 (35)
Moderate	14 (11)
Severe	4 (3)
Discomfort	
None	76 (58)
Mild	33 (25)
Moderate	15 (12)
Severe	6 (5)
Degree of correction	
None	14 (11)
Mild	45 (35)
Good	44 (34)
Excellent	27 (21)
Would have procedure again	
Yes	89 (68)
No	33 (22)
Undecided	12 (9)

TABLE 5. Areas of Treatment

Site of Injection	*Patients Treated,* n	*Average Dilution, mL*	*Average Number of Treatments*	*Patients with Nodule Formation,* n *(%)*	*Patients with Good to Excellent Results, %*
Cheeks	111	8.13	3.0	8 (7.2)	54
Temples	24	9.03	3.1	1 (4.2)	67
Nasolabial folds and marionette lines	26	9.35	3.1	1 (3.9)	62
Chest	2	12.00	1.5	0 (0)	50
Hand	8	10.25	2.5	1 (12.5)	63
Thigh	1	8.00	1	0 (0)	0
All patients	130	8.33	2.78	11 (8.5)	55

converted to lactic acid monomers and eventually eliminated as carbon dioxide, presumably through the lungs.

All cosmetic procedures carry a risk of adverse events, including but not limited to erythema, edema, bruising, bleeding, and allergic reactions. The occurrence of bruising and discomfort are mild reactions that patients should be aware of, neither of which should last more than 6 days.[16,17] Patients receiving PLLA injections should be counseled specifically on the risks of nodule formation, bruising, and discomfort. Our study demonstrated that PLLA injections were well tolerated, with a low overall side-effect profile and high patient satisfaction. Only 3% of our patient population experienced significant bruising and 5% significant discomfort. The only other large-scale, retrospective study on PLLA use in the HIV-negative, cosmetic population demonstrated a similarly low adverse-effect profile, reaffirming these results. Vleggaar[3] reported in a retrospective study of 2,131 patients that 95.1% of patients were satisfied despite an 11% incidence of hematoma formation.[3]

Subcutaneous "nodules" or "papules" are the most commonly encountered adverse event with PLLA injection.[18] A review of the PLLA literature reveals a sometimes contradictory delineation between papules, nodules, and granulomas. Some authors classify nodules into early and late onset. Early nodules are defined as small, noninflammatory nodules that occur 1 to 3 months after treatment and are spontaneously absorbed or treated using elective excision.[1] Late nodules are larger and more inflammatory, not occurring for 6 to 36 months but

TABLE 6. Characteristics of Patients Who Developed Nodules

Patient Number	*Age*	*Site of Nodule*	*Dilution Used, mL*	*Treatments,* n
1	69	Cheek (tear trough)	8	1
2	54	Temple	8	3
3	59	Cheek (left side)	8	2
4	53	Hands (bilateral)	9	1
5	58	Cheek (right side)	8	2
6	64	Marionette lines	8	4
7	58	Cheek (medial)	8	3
8	59	Cheeks (bilateral)	8	5
9	45	Cheek (right)	8	1
10	62	Cheek (left, zygomatic)	8	3
11	52	Cheek (left)	8	5
Average	57.5		8.09	2.73

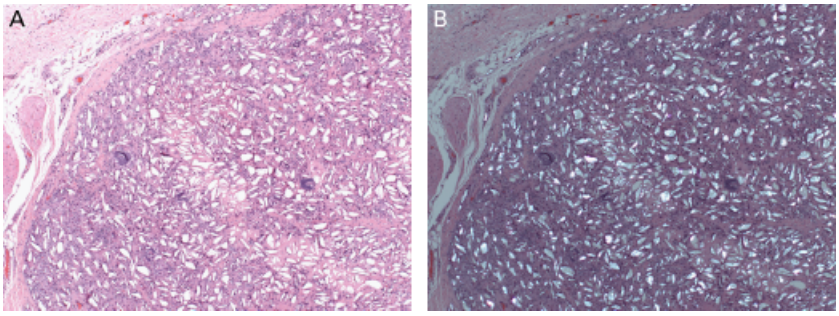

Figure 6. (A) Histopathologic appearance on hematoxylin and eosin stain of erythematous nodule biopsied from 59-year-old woman after poly-L-lactic acid depot injection to the left temple. Note the well-circumscribed dermal–subcutaneous nodule with mixed inflammatory infiltrate and foreign body giant cells. (B) Polarization of prior section with highlighting of birefringent foreign material.

appearing abruptly with accompanying edema and discoloration. They respond to intralesional steroids and show a granulomatous response upon histopathologic examination.[1,19] Late papules seem to fit the criteria of what other authors describe as "granulomas." Granulomas are characterized by their appearance under the microscope: a dense granulomatous (histiocytic and lymphocytic) inflammation with multinucleated giant cells and birefringent foreign body material.[20,21] The incidence of granulomas ranges from 0.2% to 12%, although some authors believe it is difficult to estimate the true incidence of inflammatory granuloma formation because of the scarcity of published case reports.[15] Their formation is attributed to poor injection technique, overcorrection, incorrect reconstitution, and an excessive amount of material injected.[8,19] Granulomas are treated with intralesional or oral steroids, intralesional 5-fluorouracil, oral anti-inflammatory and immunomodulatory agents, and surgical excision.[20,21]

Our interpretation of "nodules" was consistent with the most widely accepted definition as outlined by Narins[8] and Stewart and coworkers[18]: "subcutaneous papules, 5 mm or less, typically palpable but nonvisible." Nodule formation in the HIV population has varied from 6% to 52%.[6,22–25] A mixed population study by Woerle and colleagues[22] of HIV-positive patients and HIV-negative, cosmetic patients demonstrated 10% nodule formation. Similarly, Sylan[26] found a 12% incidence of granuloma formation in 100 immunocompetent patients treated with PLLA.[26] We found that, in non-immunocompromised patients, the incidence of nodule formation in this study was 8.5%, confirming the results of other studies.[27] In addition, there was no pronounced decrease in nodule incidence in our study population after the addition in 2007 of laboratory vortexing of PLLA just prior to injection. In virtually all of our patients with "nodules," papules could be palpated but were not visible. One histopathologically diagnosed case of granuloma occurred in the temporal area and was treated with subcision followed by definitive surgical excision.

In this study, patients who formed nodules had more treatments than those without nodules. Reconstitution concentrations used for patients were more dilute than the manufacturer's recommendations, at 8 mL for the cheek area and 12 mL for the chest and hands. Current recommendations in the published literature are reconstitutions of typically 5 to 10 mL. Dilution volume in our study did not appear to correlate well with the avoidance of nodule formation, although, in general, there appears to be an inverse relationship between volume dilution and the incidence of nodules; increasing volume dilution may decrease the chance of nodule formation.

The depth of injection plays an important role in minimizing nodule formation. Injections should be directed into the subcutaneous tissue rather than the lower dermis.[28,29] Superficial injections into the

lower dermis increase the likelihood of visible nodules, given the depth of placement. Our study confirms that areas such as the temple, periorbital, and perioral areas are at risk for nodule formation. Lips were not treated because the perioral region, including the upper lip area, is at high risk for nodules according to prior reports.[18] Using conservative volume amounts, a depot technique, and correct depth of placement may decrease the incidence of nodules in these sensitive areas.

Postinjection massage is also believed to decrease the occurrence of nodules by more evenly dispersing PLLA particles. Postinjection massage recommendations vary widely, from no further treatment beyond the in-office physician massage to continued patient massage for up to 1 month after treatment.[30] We recommend the "5-5-5" rule to patients: firm manual massage for 5 minutes, five times a day, for 5 days.

Patient satisfaction for the procedure was high, with an overall good to excellent correction result in 55% of patients. The temples, hands, and nasolabial folds and marionette lines received the highest level of satisfaction from patients. Although the hand had the highest incidence of nodule formation, it provided one of the highest degrees of patient satisfaction, perhaps because volume repletion in this area can be dramatic, restoring a more voluminous, youthful appearance. Lastly, patient satisfaction was correlated with a greater number of treatments and was up to 75% for those receiving five or more treatments. This trend may also demonstrate that patients who had a positive response to PLLA continued to seek additional treatment sessions, whereas others who did not see enough visible improvement from PLLA declined further treatment. It is therefore important to adequately counsel patients that they must anticipate multiple vials or sessions to acquire full satisfaction with volume repletion in the area treated.

There are limitations to our study. It was retrospective in nature and relied on patient recollection. As many as 10% of patients identify papules early on in PLLA treatment,[1] so patient's perceptions of these transient irregularities or misdiagnosed skin lesions believed to be "nodules" may have artificially inflated our incidence of nodules. However, the treating physician examined all patient-reported nodules in clinic, reducing reporting error of this PLLA adverse event. Furthermore, a small sample size may have skewed the higher incidence of nodules in areas such as the hands rather than reflecting the true incidence of nodule formation in this area. Our study did not examine duration of response, although this was indirectly examined according to patient satisfaction. Additional studies examining the duration of effect will allow a comparison between immunocompetent, cosmetic patients and the HIV-positive population, for which facial volume is maintained for at least 2 years after PLLA treatment.[18] Although our study of 130 patients is the largest of cosmetic PLLA use in an HIV-negative population, a larger, prospective trial is necessary to further explore patient satisfaction and adverse events associated with cosmetic PLLA use.

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