A Randomized, Split-Body, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Poly-L-lactic Acid for the Treatment of Upper Knee Skin Laxity

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BACKGROUND Skin laxity of the upper knee and lower thigh is a common complaint among patients.

OBJECTIVE This is a randomized, double-blinded, split-body, placebo-controlled study to evaluate the safety and efficacy of poly-L-lactic acid (PLLA) for treatment of upper knee skin laxity.

MATERIALS AND METHODS Twenty female subjects between the ages of 30 and 65 years with upper knee laxity were enrolled. The patients were randomized to receive 3 treatments of PLLA in 1 knee, whereas the other knee received 3 treatments of bacteriostatic water.

RESULTS Statistically significant improvement as rated on the physician global aesthetic improvement scale was seen at Day 56 after final treatment in the active knee when compared with the placebo knee. This improvement was sustained at Day 84 and Day 168 after final treatment visits. No statistically significant difference was seen between the active and placebo knees on the subject global aesthetic score or the subject satisfaction scale.

CONCLUSION Based on our study, PLLA may be a safe and effective modality in addressing upper knee skin laxity. Larger studies with longer follow-up times and a validated knee laxity scale are needed to further determine if and how much improvement can be achieved.

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Skin laxity of the upper knee and anterior thigh is a common complaint among patients. Safe and effective treatment options for upper knee laxity are scarce. Microfocused ultrasound with visualization has recently been shown to be effective for reducing skin laxity and crepiness of the knee but requires capital equipment. Microfocused ultrasound has shown to induce lifting and tightening by thermocoagulation of old collagen and stimulation of new collagen production.[1]

Because poly-L-lactic acid (PLLA; Sculptra Aesthethic; Galderma Laboratories, Fort Worth, TX) stimulates neocollagenesis, it is possible it may be beneficial in the treatment of lax skin of the knee. Poly-L-lactic acid is an injectable implant containing microparticles of PLLA, carboxymethylcellulose, and nonpyrogenic mannitol. It is currently approved by the FDA for the correction of shallow to deep nasolabial fold contour deficiencies and other facial wrinkles in immune-competent patients and for facial lipoatrophy in patients with HIV.[2] Poly-L-lactic acid microspheres

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ORIGINAL CONTRIBUTION

Clinical experience of poly-L-lactic acid injections for body contouring treatment

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Abstract

Introduction: Clinical data on body contouring with injectable poly-L-lactic acid are sparsely reported in published literature. This study describes the lead author's clinical experience using injectable poly-L-lactic acid for body contouring in various anatomic locations.

Methods: Twenty consecutive patients undergoing body contouring treatments with poly-L-lactic acid were prospectively followed. All treatments were performed at a single clinic between February 2017 and February 2019. Treatment details such as reconstitution, injection volume and dosage were documented. Treatment response was assessed independently by patients and the treating physician. Adverse events were recorded.

Results: Twenty patients (85% women) received injectable poly-L-lactic acid for body contouring treatments such as buttocks volumization, cellulite and skin quality treatment. In most patients (65%), poly-L-lactic acid was administered to correct postsurgical soft tissue deformities. Overall, patients had a mean of 5.1 treatment sessions in a mean of 1.4 anatomic locations. The most commonly treated anatomic locations were buttocks (58% of treatment sessions), thighs (20%) and abdomen (9%). Dosage and injection volume varied between patients depending on anatomic location and desired outcome. Most treatment sessions (86%) resulted in improvement of the treated area. Adverse events included bruising, oedema, numbness and tenderness. Nodule formation was recorded for one patient (5%).

Conclusion: According to the lead author's clinical experience, poly-L-lactic acid injection is well tolerated and can achieve good aesthetic outcomes when used for body contouring in appropriate patients. Preliminary data suggest that poly-L-lactic acid injection may be a viable nonsurgical technique for correcting postsurgical soft tissue deformities.

KEYWORDS
biostimulator, body contouring, PLLA, poly-L-lactic acid, sculptra aesthetic, volumizers

1 | INTRODUCTION

Historically, rejuvenating or improving the aesthetic appearance of the face and body has relied upon invasive cosmetic procedures. However, recent decades have seen rapid technological advancement and expansive application of nonsurgical aesthetic procedures that are delaying and, in some cases, eliminating the need for surgical intervention. As the safety and efficacy of nonsurgical modalities have become increasingly reliable and predictable, the demand for noninvasive or minimally invasive treatments has substantially increased.[1] To date, available data on injectable aesthetic procedures predominantly focus on facial rejuvenation and improvement. However, as nonsurgical aesthetic treatments continue to procure additional and expanded indications, there is growing interest in the use of aesthetic injectables to treat nonfacial regions of the body.[2]

Injectable poly-L-lactic acid (PLLA) is of particular interest, as this biostimulatory agent has physiochemical properties that are distinct from other common dermal fillers. Injectable PLLA (Sculptra Aesthetic, Galderma Laboratories) is a synthetic, biodegradable material comprised of PLLA microparticles, carboxymethylcellulose and nonpyrogenic mannitol that is indicated for the correction of facial wrinkles and nasolabial fold contour deficiencies.[3] Following injection, the PLLA microparticles elicit a mild inflammatory response in the host, which causes downstream collagen deposition in the area of injection.[4] The gradual deposition of neocollagen promotes tissue remodelling and volume restoration, yielding effects that have greater longevity compared to replacement fillers such as hyaluronic acid fillers.[4] In most countries, including the United States, nonfacial applications of injectable PLLA are considered off-label and its use for treating body contour deficiencies has not been extensively studied in clinical trial settings. Most of the published data on body treatments with PLLA stem from case series on neck, décolletage, arm and hand treatments.[5–8] Two open label studies describe the use of PLLA for treating photodamage and rhytids of the décolletage and sagging skin.[9,10] While these studies report favourable outcomes, research and data on the use of PLLA in nonfacial regions are limited. Further studies with larger sample size, blinding, control arms and longer duration of follow-up would be valuable.

Herein, the lead author presents his clinical experience with nonfacial applications of injectable PLLA for body contouring, buttocks volumization, cellulite and skin quality improvement, and the correction of postsurgical soft tissue deformities.

2 | METHODS

The data presented here are based on the lead author's clinical experience with PLLA injection for nonfacial body contouring. All treatments were performed at a single clinic between February 2017 and February 2019, in accordance with routine clinical practice. Patients were educated on the risks and benefits of treatment and provided informed consent prior to first injection.

2.1 | Patients

Adult patients seeking nonsurgical body contouring treatments such as buttocks volumization, cellulite and skin quality improvement, and correction of postsurgical soft tissue deformities were included in the study. Of note, all patients included in this study requested nonsurgical management of their aesthetic concern(s) and were not interested in undergoing surgery. Contraindications included hypersensitivity to any of the components of injectable PLLA and known history of or susceptibility to keloid formation or hypertrophic scarring.

2.2 | PLLA Preparation

Each vial of PLLA (Sculptra Aesthetic, Galderma Laboratories) was reconstituted with bacteriostatic sterile water for injection (BSWFI). A minimum of 2 hours after reconstitution with BSWFI, lidocaine (1–2%) with epinephrine was added. Within 1 hour of adding lidocaine with epinephrine, the vial was gently agitated, and syringes for injection were prepared.

Treatment details were documented for each treatment session including reconstitution volume, total injection volume and dosage. Dosage and total injection volume varied between patients and was dependent on anatomic location and the extent of contour deformity. Total injection volume (BSWFI: lidocaine [1–2%] with epinephrine) per vial of PLLA was either 7 mL (5 mL: 2 mL), 10 mL (8 mL: 2 mL), 10.5 mL (10 mL: 0.5 mL), 14 mL (12 mL: 2 mL) or 15 mL (13 mL: 2 mL). (Table 1 and Table 2).

For most treatment locations, the total injection volume was either 10 mL or 15 mL per vial of PLLA. For volumization treatments, a more concentrated formulation (10 mL total injection volume per vial of PLLA) was generally used to allow placement of a greater volume in the target area with less product spread. For cellulite treatments, a more dilute formulation (15 mL total injection volume per vial of PLLA) was generally used.

Prior to injection, the treatment area was inspected and verified to be free from inflammation and infection. The skin was prepped with chlorhexidine-alcohol and treatment was conducted with aseptic technique.

2.3 | PLLA injection technique

Prior to injection of PLLA, needle aspiration was performed to minimize the risk of inadvertent intravascular injection. The reconstituted PLLA was administered using a slow, low pressure, retrograde injection method. The PLLA suspension was deposited with 23-25G 1.5 inch sterile needles using deep dermal threading or tunnelling grid pattern (cross-hatching) techniques. Volumization treatments involved deep dermal or subdermal injection planes, irrespective of the anatomic location. Cellulite, stretch marks and skin quality treatments involved slightly more superficial injections to the

TABLE 1 Specification of treatment sessions with PLLA in 20 patients

Area	No. of patients treated	Total no of treatment sessions[a]	No. of treatment sessions per patient		Days between treatment sessions[b]	
	N	*n*	Mean (*SD*)	Median (range)	Mean (*SD*)	Median (range)
Buttocks	16	59	3.7 (2.8)	2.5 (1–11)	69.3 (41.4)	56.0 (29–168)
Thigh	4	21	5.3 (5.3)	3.0 (2–13)	53.2 (27.0)	48.1 (27–90)
Abdomen	3	9	3.0 (2.6)	2.0 (1–6)	95.6 (7.9)	95.6 (90–101)
Knee	2	3	1.5 (0.7)	1.5 (1–2)	47.0 (--)	47.0 (47–47)
Arm	1	2	2.0 (--)	2.0 (2–2)	69.0 (--)	69.0 (69–69)
Hand	1	1	1.0 (--)	1.0 (1–1)	--	--
Supraumbilical cavity	1	7	7.0 (--)	7.0 (7–7)	51.3 (--)	51.3 (51–51)

--: not applicable, SD: standard deviation

[a]Left and right side counted separately

[b]Patients with more than one treatment session: buttocks (n = 13), thigh (n = 4), abdomen (n = 2), knee (n = 1), arm (n = 1), hand (n = 0), supra umbilical concavity (n = 1)

TABLE 2 Specification of PLLA treatments and outcomes in 20 patients

Area	Total no.of treatment sessions[a]	No. of PLLA vials per treatment session		Total injection volume[b] per vial of PLLA		Treatment sessions assessed as improved		
	n	Mean (SD)	Median (range)	Volume[c]	*n* (%)	Yes *n* (%)	No *n* (%)	UNK *n* (%)
OVERALL	102	6.4 (5.7)	6.0 (1–40)	5 mL 7 mL 10 mL 10.5 mL 14 mL 15 mL	1 (1) 5 (4.9) 43 (42.2) 5 (4.9) 3 (2.9) 45 (44.1)	88 (86.3)	6 (5.9)	8 (7.8)
Buttocks	59	8.6 (6.4)	8.0 (1–40)	7 mL 10 mL 10.5 mL 14 mL 15 mL	1 (1.7) 22 (37.3) 1 (1.7) 1 (1.7) 34 (57.6)	48 (81.3)	5 (8.5)	6 (10.2)
Thigh	21	4.1 (2.6)	4.0 (1–9)	10 mL 10.5 mL 14 mL 15 mL	12 (57.1) 3 (14.3) 2 (9.5) 4 (19.0)	21 (100)	--	--
Abdomen	9	1.6 (0.9)	1.0 (1–4)	10 mL 15 mL	4 (44.4) 5 (55.6)	7 (77.8)	1 (11.1)	1 (11.1)
Knee	3	5.2 (1.4)	6.0 (4–6)	10 mL	3 (100.0)	2 (66.7)	--	1 (33.3)
Arm	2	6.0 (0.0)	6.0 (6–6)	10 mL 10.5 mL	1 (50.0) 1 (50.0)	2 (100)	--	--
Hand	1	2.0 (--)	2.0 (2–2)	5 mL	1 (100.0)	1 (100)	--	--
Supraumbilical cavity	7	2.6 (0.5)	3.0 (2–3)	7 mL 10 mL 15 mL	4 (57.1) 1 (14.3) 2 (28.6)	7 (100)	--	--

--: not applicable, SD: standard deviation, UNK: unknown

[a]Left and right side counted separately

[b]Bacteriostatic sterile water for injection (BSWFI) + lidocaine 1–2% with epinephrine (LPE)

[c]7 mL = 5 mL BSWFI + 2 mL LPE;10 mL = 8 mL BSWFI + 2 mL LPE;10.5 mL = 10 mL BSWFI + 0.5 mL LPE;14 mL = 12 mL BSWFI + 2 mL LPE;15 mL = 13 mL BSWFI + 2 mL LPE.

mid-to-deep dermis. Care was taken to maintain a sufficient depth of injection, avoiding injection to the superficial layers of the dermis. Superficial injections can cause a dermal wheal or peau d'orange skin changes and may be associated with increased local adverse events such as nodules and papules. Target treatment areas were undercorrected to allow for an expected gradual restoration of volume over several weeks.

2.4 | Posttreatment care, follow-up and outcomes

After injection, the treated area was massaged to distribute the PLLA evenly, and ice-packs were applied to minimize postinjection discomfort. Patients were instructed to massage the treated area during the first five days following injection; to minimize sun exposure of the treated area; and to avoid UV lamp exposure until any swelling and redness had resolved. Follow-up visits were performed at an interval of at least 3 weeks.

Adverse events were recorded during each treatment session and at follow-up visits. Standard 2-D photography with uniform lighting, background and camera (digital single-lens reflex) was employed, capturing multiple angles of the target treatment area. Treatment outcomes were assessed independently by patients and the treating physician via comparison of pre- and posttreatment photographs taken at baseline and after the final treatment session. Improvement was defined as volumization and/or increased visible fullness of the injected area. Agreement between patient-reported and physician-reported outcome was required for the treatment area to be rated as improved.

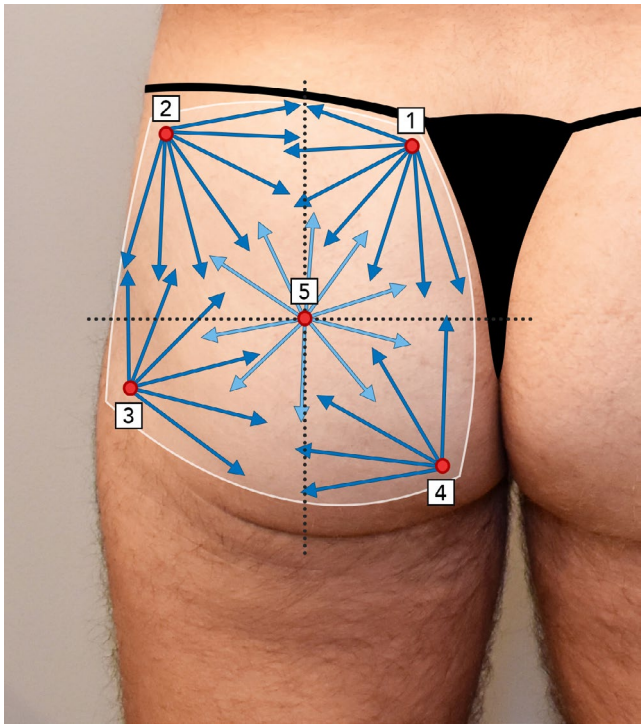

FIGURE 1 Injection technique for buttocks augmentation with PLLA. Posterior view of the gluteal region illustrating the zone of treatment, port sites and injection pattern. White lines indicate the boundaries of the gluteal treatment zone. Five port sites (shown as red points) are utilized per buttock; port sites are located at the upper medial quadrant (1), upper lateral quadrant (2), lower lateral quadrant (3), lower medial quadrant (4), and at the axes intersection point (5). The cannula is inserted through each port site and advanced along the path of the blue arrows in a fan-like manner

3 | RESULTS

3.1 | Demographics

Twenty patients with a mean age of 41 years (range 27–54) and a mean body mass index of 22 kg/m^2 (range 18–30) were treated with injectable PLLA for body contouring. Most patients were women (85%), White (55%) or Hispanic (15%). The majority of patients (80%) had undergone previous aesthetic procedures.

3.2 | Treatments

Twenty patients underwent a total of 102 treatment sessions with injectable PLLA for soft tissue body contouring. PLLA injections were primarily used for volumization of buttocks as well as cellulite and skin quality improvement. Thirteen patients (65%) were treated with injectable PLLA to correct soft tissue contour deformities occurring as a result of prior aesthetic surgery; 12 patients were treated for contour deformity secondary to surgical liposuction, and one patient was treated for abdominal wall deformity secondary to abdominoplasty surgery. Overall, patients had a mean of 5.1 treatment sessions in a mean of 1.4 anatomic locations. The most commonly treated anatomic locations were the buttocks (58% of treatment sessions), thighs (20% of treatment sessions) and abdomen (9% of treatment cycles); 13% of treatment sessions involved other anatomic locations including the knees, arms, hands and supra-umbilical region. Dosage and total injection volume varied between patients depending on the anatomic location and desired outcome. Overall, patients received an average of 6.4 vials of PLLA per treatment session. For the most commonly treated anatomic locations, the mean number of PLLA vials administered per treatment cycle was 8.6 (buttocks), 4.1 (thigh) and 1.6 (abdomen). Table 1 and Table 2 present an overview of all treatments.

3.3 | Treatment effect

Most treatment sessions (86%) resulted in improvement of the treated area. All treatment sessions that did not result in improvement (6%) were initial treatments. For the remaining 8% of treatment sessions, improvement data were not available due to patients being lost to follow-up.

Figure 1 and Figure 2 illustrate the injection technique (Figure 1) and treatment outcome (Figure 2) for buttocks volumization treatment with PLLA. Figure 3 demonstrates the treatment outcome for

PLLA injections to the abdomen for the correction of postsurgical contour deformities.

3.4 | Safety

3.4.1 | Solicited adverse events

Solicited injection-site adverse events (AEs) including bruising, oedema, numbness and tenderness were collected in 19 patients. All 19 patients reported incidence of bruising, oedema, tenderness and numbness, which resolved within an average period of 4, 3, 3 and 2 days, respectively. Safety data was not available for one patient who was lost to follow-up.

3.4.2 | Unsolicited adverse events

One patient (5%) reported a nodule of mild severity after initial treatment of the left buttocks with one vial of PLLA reconstituted in 5 mL BSWFI and 2 mL lidocaine (1%) with epinephrine. The nodule resolved spontaneously after 38 days.

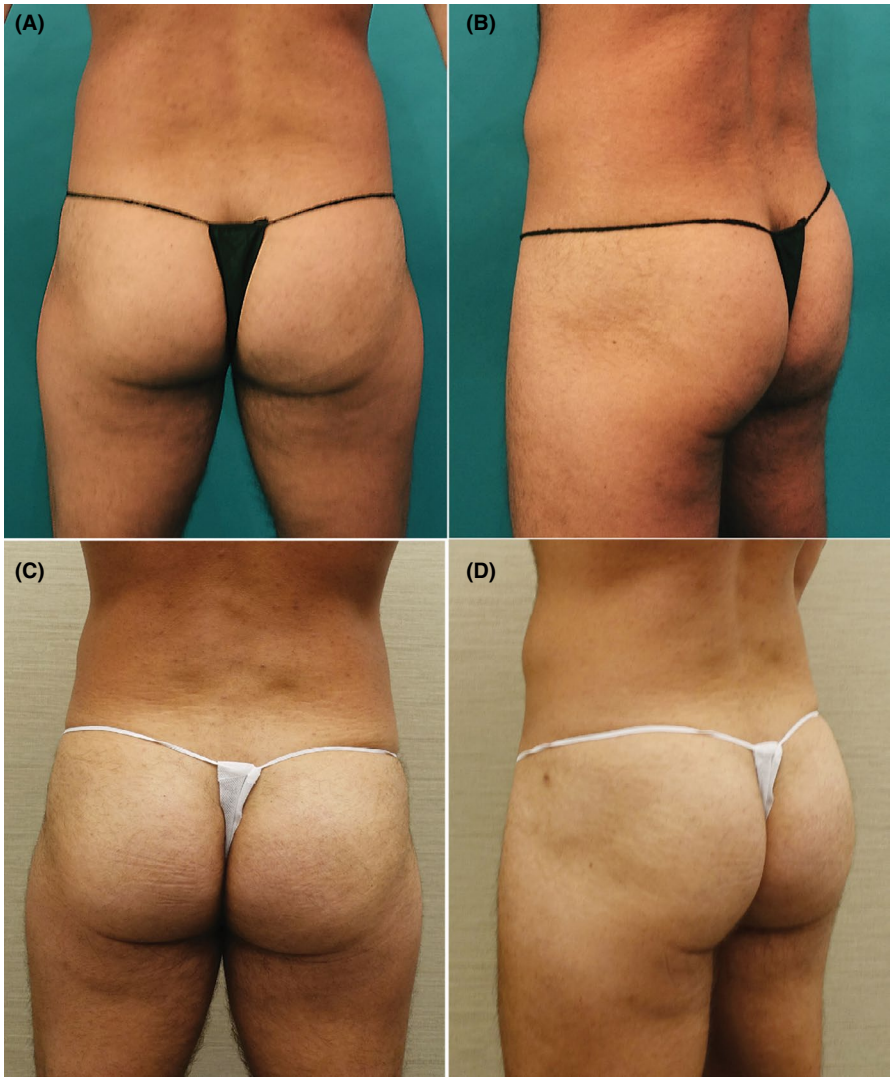

FIGURE 2 Case description of buttocks volumization treatment with PLLA. (A) and (B) Pretreatment photographs of a 38 year-old man requesting buttocks volumization. The patient underwent six total treatment sessions with injectable PLLA to the buttocks. At the first treatment session, four total vials of PLLA were administered (two vials per side, each vial reconstituted with 12 mL BSWFI + 2 mL lidocaine [1%] with epinephrine). At subsequent treatment sessions, 4–6 total vials of PLLA were administered per session (2–3 vials per side, each vial reconstituted in 13 mL BSWFI + 2 mL lidocaine [2%] with epinephrine). The re-treatment interval was approximately 1–2 months for the second to fifth treatments, and approximately 6 months for the sixth treatment. (C) and (D) Posttreatment views taken at first occasion of optimal correction with high patient satisfaction, approximately 17 months after the first treatment session and 6 months after the sixth PLLA treatment session. Both the patient and treating physician assessed that all treatment sessions resulted in aesthetic improvement of the buttocks. The patient experienced solicited adverse events (bruising, oedema, numbness and tenderness) which resolved within 1 week; no additional adverse events occurred

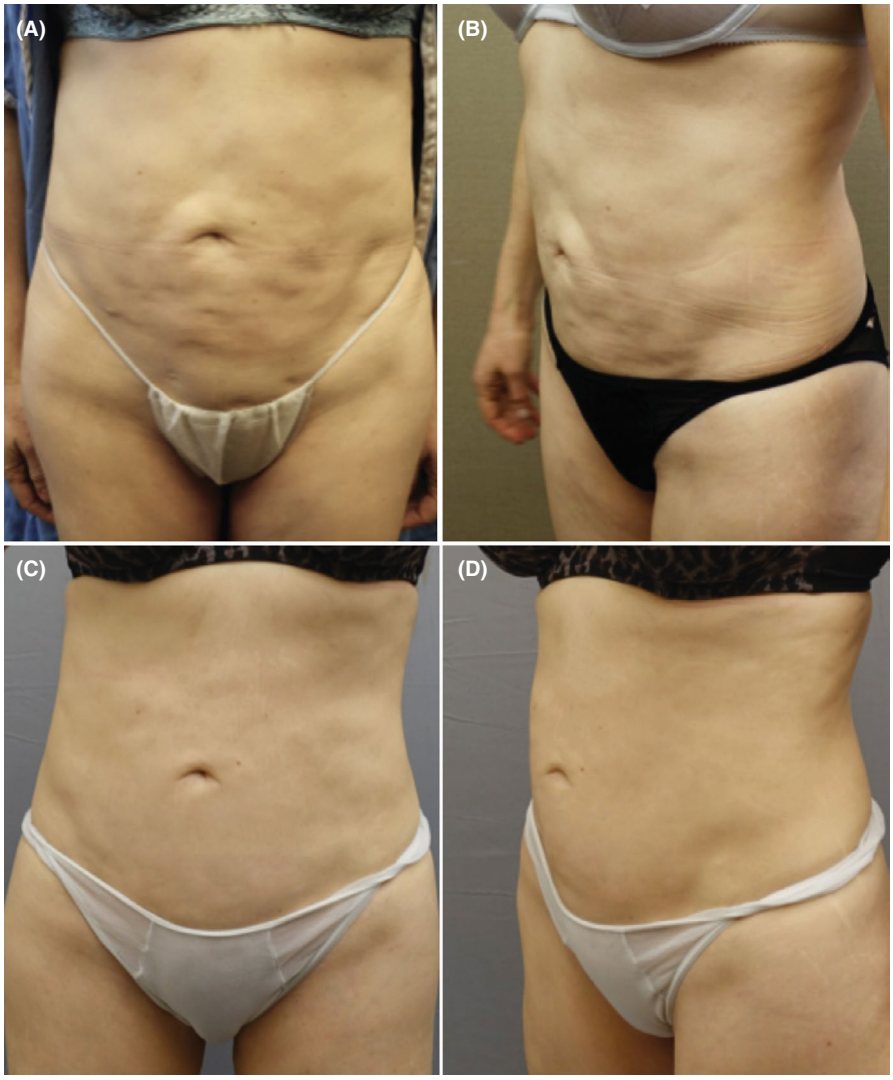

FIGURE 3 Case description of PLLA injection for the correction of postsurgical contour deformity. (A) and (B) Pretreatment views of a 54 year-old woman requesting treatment for abdominal soft tissue contour deformity secondary to previously performed abdominal liposuction. The patient underwent six total treatment sessions with injectable PLLA to correct the postsurgical contour deformity. At the first treatment session, one total vial of PLLA was administered to the abdomen (0.5 vial per side, reconstituted in 13 mL BSWFI + 2 mL lidocaine [2%] with epinephrine). At subsequent treatment sessions, 1–2 total vials of PLLA were administered per session (reconstituted in 13 mL BSWFI + 2 mL lidocaine [1–2%] with epinephrine). The re-treatment interval was approximately 1–2.5 months for the second to fifth treatment sessions, and approximately 10 months for the sixth treatment session. (C) and (D) Posttreatment views taken at first occasion of optimal correction with high patient satisfaction, approximately 22 months after the initial treatment session and 5 months after the sixth treatment session. Except for the initial treatment session which did not result in visible improvement of the abdomen, all subsequent treatment sessions resulted in aesthetic improvement, as assessed by both the patient and treating physician. The patient experienced solicited adverse events (bruising, oedema, numbness and tenderness) which resolved within one week; no additional adverse events occurred

4 | DISCUSSION

As minimally invasive techniques continue to develop and gain increased popularity,[11] practitioners should stay well-informed about the broad range of procedures available and the efficacy of their use. Many widely known nonsurgical modalities that were initially developed for aesthetic improvement of the face are being used with expanded applicability to treat nonfacial regions of the body. While injectable PLLA is currently approved in most countries for the correction of facial rhytids and folds, there is increasing interest in the use of PLLA for nonfacial body contouring.[3] Numerous studies have described the use of injectable PLLA for facial rejuvenation, and several techniques have been introduced to optimize safety and improve outcomes. However, studies describing the use of PLLA for soft tissue contouring in off-face areas of the body are limited.

PLLA has several benefits over other injectable volumizing agents that are currently available. The effects of replacement fillers, such collagen and HA-based fillers, are dependent on the space-filling capacity of the injected material itself. That is, the efficacy of replacement fillers is a function of the substance's ability to directly fill the

soft tissue. Injectable PLLA, on the other hand, is a biostimulatory agent. Upon injection, the PLLA microparticles induce a subclinical inflammatory response and stimulate neocollagen production in the extracellular matrix, which results in gradual volumization, improved skin texture and increased skin thickness via tissue remodelling.[4] In this way, the cosmetic effects of injectable PLLA are dependent on the host response, rather than the space-occupying properties of the injected substance. Furthermore, the volume restoration achieved with injectable PLLA occurs in a controlled and predictable manner, offering results that last for up to 2 years.[4]

All of the patients included in this study were seeking nonsurgical management of their aesthetic concerns and were fundamentally disinterested in undergoing surgery. Notably, a large cohort of patients (65%) underwent treatment to correct soft tissue deformities resulting from previously performed aesthetic surgery such as liposuction and abdominoplasty. For these patients, given that prior surgery had caused the contour irregularity of concern, nonsurgical intervention was of paramount importance. Most PLLA treatment sessions (86%) resulted in aesthetic improvement of the affected area, as determined by both the patient and practitioner. These findings suggest that PLLA injection may be an appropriate treatment option for patients with both cosmetic and correctional treatment goals who prefer nonsurgical techniques.

The safety profile of PLLA in this study was congruent with that described in the product label, with the exception of temporary posttreatment numbness. Because all instances of numbness were transient and resolved within an average of 2 days postinjection, the authors believe that posttreatment numbness was likely attributable to the addition of lidocaine during PLLA reconstitution.[3] One patient reported the presence of a nodule at the injection site that resolved approximately 8 weeks posttreatment.

The pretreatment consultation is an important component of PLLA treatment, especially in patients concerned with postsurgical contour deformities. Prior to treatment, patients should understand that the increase in volume observed immediately following injection is due to mechanical distention from the injected PLLA suspension and will decrease over several days as the formulary water is absorbed by the bod; patients should recognize that the outcomes achieved with PLLA are not immediate and appear gradually over time. Managing patient expectations is particularly important in patients with a history of HA filler injections who may anticipate visible results immediately postinjection. Additionally, patients should understand that PLLA achieves a subtler volumization effect as compared to large volume fat transfer or permanent implants.

It is important for clinicians to counsel patients on the PLLA treatment protocol, which generally occurs over several months and requires multiple treatment sessions. The lead author's treatment protocol typically involves 2–3 treatment sessions spaced 4–6 weeks apart, followed by a period of 3–6 months over which the final volumetric effects will develop. Anecdotally, older patients (aged ≥ 60 years), and those who have moderate to severe skin laxity or subcutaneous fat volume loss, often require an increased number of treatment sessions and/or larger volumes of PLLA per session to achieve optimal correction. As with other dermal fillers, longevity of effect and preservation of treatment outcome requires recurrent treatment with injectable PLLA. Intermittent 'booster' treatments in which smaller volumes of product are administered may be used to prolong the effects of treatment. Finally, patients should be informed that full predictability with respect to treatment outcome and the number of treatment sessions required is not feasible, as neocollagen formation is slightly different in each patient.

Nonfacial applications of injectable PLLA have several limitations that warrant mention. It is important to note that the results achieved with PLLA injection are not reversible. As such, undertreating the target area is essential for avoiding complications and unfavourable outcomes. This strategy, however, increases the likelihood that patients will require a greater number of treatment sessions to obtain optimal volumization.

Additionally, the authors recognize that the volume of PLLA required to achieve the outcomes highlighted in this article may be prohibitively expensive or financially burdensome for the patient. Considering the current cost of product, favourable applications for nonfacial PLLA may involve localized contour irregularities and regions of the body with a small surface area. Nevertheless, because the patients included in this study did not wish to pursue surgical intervention, an injectable treatment such as PLLA was the only means of addressing their aesthetic concerns. The primary purpose of this study was to present preliminary data on the safety, effectiveness and feasibility of injectable PLLA in off-face areas of the body.

The limitations of this study include a small sample population, a limited follow-up period, and the lack of a validated assessment tool for soft tissue volumization. In this study, treatment response was determined by patient- and physician-reported assessments of pre- and posttreatment photographs, and the lack of precise quantification of soft tissue volume changes limits our findings. Further studies that include high-definition imaging, 3-D greyscale and validated scales for aesthetic assessment such as the Hexsel photonumeric Cellulite Severity Scale (CSS) are needed to support our findings.

In this prospective, interventional study, the use of PLLA for soft tissue contouring in nonfacial areas of the body was effective and well-tolerated. Our findings suggest that PLLA injection should be considered a viable nonsurgical modality for improving the appearance of soft tissue irregularities and/or depressions in off-face regions. Additional research and data from well-controlled clinical trials are warranted to inform best practice guidelines and determine the long-term safety, efficacy and longevity of PLLA in nonfacial areas of the body.

5 | CONCLUSION

According to the lead author's clinical experience, PLLA injection is effective and well-tolerated when used for body contouring and correcting postsurgical soft tissue deformities in appropriate patients. The use of injectable PLLA to augment and restore volume

in nonfacial regions of the body represents a promising minimally invasive alternative to surgical techniques for body contouring.

CONFLICT OF INTEREST

S.M. Shridharani is an advisory board member, speaker and investigator for Galderma. C. Edwartz is employed by Galderma Aesthetics.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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ORIGINAL ARTICLE
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Consensus Recommendations on the Use of Injectable Poly-L-Lactic Acid for Facial and Nonfacial Volumization

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ABSTRACT

Poly-L-lactic acid (PLLA) was approved for use in Europe in 1999. In the United States, it was approved by the Food and Drug Administration in 2004 for the treatment of facial lipoatrophy associated with human immunodeficiency virus, and in 2009 for cosmetic indications in immune-competent patients. The need for consistent, effective PLLA usage recommendations is heightened by an increased consumer demand for soft tissue augmentation and a shift toward a younger demographic. Over the past 14 years, considerable experience has been gained with this agent, and we have come to better understand the clinical, technical, and mechanistic aspects of PLLA use that need to be considered to optimize patient outcomes. These consensus recommendations regarding patient selection, proper preparation and storage, optimal injection techniques, and other practical considerations reflect the body of evidence in the medical literature, as well as the collective experience of this author group.

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INTRODUCTION

Poly-L-lactic acid (PLLA) was approved for use in Europe in 1999. In the United States, it was approved by the Food and Drug Administration in 2004 for the treatment of facial lipoatrophy associated with human immunodeficiency virus (HIV),[1] and in 2009 for cosmetic indications in immune-competent patients.[2] Over the past 14 years, considerable experience has been gained with PLLA; and its safe and effective use has been well documented.[3-24]

The need for consistent, effective usage recommendations is heightened by an increased consumer demand for soft tissue augmentation, and a shift toward a younger demographic that may have a lower tolerability for adverse events.[25,26] The demonstrated preference of patients for gradual, long-lasting effects[27,28] is well matched to the mechanism of action of PLLA,[7,29-31] which provides distinct clinical advantages over other available options, including cosmetic benefits lasting 2 years or more.[1,29]

Our detailed review of the literature reveals that most of the early problems encountered with PLLA resulted from suboptimal methodology, including inadequate reconstitution volumes, short hydration times, injection of large volumes of highly concentrated product with short intervals between treatments, and injection into the dermis and in locations that were not optimally chosen vis-à-vis its mechanism of action.[5,6,9,12,18,32] As clinical experience has grown, we have come to better understand the technical and mechanistic aspects of PLLA use that need to be considered to optimize patient outcomes (Table 1). With this enhanced understanding, PLLA utilization can now achieve predictable cosmetic benefits that are completely controlled by the treating clinician.

The consensus recommendations that follow reflect the body of evidence in the medical literature, as well as the collective experience of this author group, each of whom have more than a decade of experience in the clinical utilization of PLLA.

Patient Selection

As with all cosmetic procedures, it is important that there be clear communication between physician and patient (Table 1). In addition, patients should be well matched to the mechanism of action and clinical effects of the treatment.

- Patients should have realistic treatment goals, be educated on aging-associated volume loss and the gradual nature of PLLA cosmetic benefits, and understand the need for multiple treatment sessions and periodic maintenance for an enduring effect.
- Experience with facial augmentation has taught us that patients with very empty faces or those with a very elastotic outer skin envelope may be challenging to volumize, requiring a substantial amount of product, any product, to achieve a desirable result. This should be expected in this patient population and discussed prior to any filler treatment to prevent unnecessary frustration on the part of both the patient and the physician.
- Patients are starting cosmetic treatments earlier than they have traditionally done. The 2012 American Society of Plastic Surgeons statistics revealed that 66% of cosmetic patients are now between the ages of 30 and 54, while only 26% are age 55 or older. This younger group often needs less product and fewer treatment sessions than the older group, and is gratifying to treat.[33]
- Patients with permanent fillers, or active auto-immune or connective tissue disease (eg, multiple sclerosis, lupus) may be less predictable hosts.
- Active granulomatous disease should be considered a contraindication to PLLA use.

Poly-L-Lactic Acid Preparation and Storage

Recommendations on the preparation and storage of PLLA focus on ensuring complete and homogenous dispersion and hydration of PLLA in sterile water for injection (SWFI) or bacteriostatic water, in a volume that facilitates injection (Table 2).

- Reconstitution/Dilution
  - Prior to reconstitution, tap the vial to ensure there is no powder sticking to the top of the vial or rubber stopper.
  - Use an antiseptic to clean the rubber stopper.
  - Add 7–8 mL SWFI or bacteriostatic water slowly to the powder.
    - Dilution in this volume range leads to:
      - Even PLLA distribution.
      - Easier injection, with reduced risk of needle blockage.
      - Decreased incidence of papules and nodules.
- Hydration
  - Hydrate at room temperature for ≥24 hours.
    - Adequate powder hydration allows the avoidance of injecting dry PLLA microclumps, which will hydrate in vivo and potentially lead to nodule formation.
  - Do NOT shake the vial during hydration.
    - Shaking can result in the deposition of dry PLLA clumps on the vial wall.
- Storage of reconstituted PLLA
  - Prior to use, reconstituted PLLA can be stored for up to:
    - 48 hours at room temperature.
    - 3–4 weeks in a refrigerator (4°C) [with bacteriostatic water]

Final Poly-L-Lactic Acid Preparation

Final steps prior to injection should ensure a hygienic approach and a smooth injection process.

- Patient/Clinician (Table 1)
  - Patients should wash their face with soap and water.
  - The clinician should wipe the areas for injection with chlorhexidine/alcohol immediately prior to injection to reduce risk of infection or biofilm formation.
- PLLA preparation
  - Warm the PLLA solution to room temperature (if stored at 4°C).
  - Dilute to final injection volume.
    - For facial injections, a final dilution of 9 mL is recommended, and may be achieved by the addition of 1–2 mL lidocaine (with or without epinephrine).
    - For décolletage injections, a final dilution of 11–16 mL is recommended, and may be achieved by further dilution with addition al SWFI or bacteriostatic water and 1–2 mL lidocaine (with or without epinephrine).
  - Ensure product is evenly suspended by slowly rolling the vial; do not shake. Shaking can create foam, which may clog the needle.

Poly-L-Lactic Acid Injection and Aftercare

Key factors in the utilization of PLLA include site selection (Table 1); injection depth, quantity, and frequency; and aftercare, as well as other practical considerations (Table 3).

Injection Site Selection

Injection sites associated with the most favorable outcomes are dynamically stable, with sufficient dermal thickness to allow a proper depth of injection.

TABLE 1.

Optimizing Results With Poly-L-Lactic Acid

Category	Tip
Patient Interactions	• Reinforce the goals of PLLA use (eg, deep, global volumization), as compared with other treatments. • Use diagrams to demonstrate expected cosmetic changes. • Calibrate expectations regarding the gradual nature of the cosmetic enhancement. • Document cosmetic changes with photographs (at baseline and each subsequent visit).
Product Handling	• Warm PLLA to body temperature before injection to facilitate injection. • Avoid agitation immediately prior to injection to decrease risk of clogging. • If foaming is an issue, remove the rubber stopper and slowly draw product out of the vial.
Injection Techniques	• Understand facial anatomy to avoid injection in or too close to blood vessels. • Apply a thin, uniform coating to entire surface of the treatment region. • Treat, wait, and assess; avoid over-application within a single session to decrease risk of overcorrection.

PLLA, poly-L-lactic acid

TABLE 2.

Poly-L-Lactic Acid Preparation and Storage

Step	Recommendations
Reconstitution/Dilution	• Ensure there is no powder sticking to the top of the vial or rubber stopper. • Use an antiseptic to clean the rubber stopper. • Slowly add 7–8 mL sterile water for injection or bacteriostatic water.
Hydration	• Hydrate at room temperature for ≥24 hours. • Do NOT shake the vial during hydration.
Storage of Reconstituted Poly-L-Lactic Acid	• 48 hours at room temperature. • 3–4 weeks in a refrigerator (4°C).
Final Injection Volume for Facial Treatment	• 9 mL, achieved by the addition of 1–2 mL lidocaine (with or without epinephrine) immediately prior to injection.
Final Injection Volume for Décolletage Treatment	• 11–16 mL, achieved by further dilution with additional SWFI or bacteriostatic water and 1–2 mL lidocaine (with or without epinephrine) immediately prior to injection.

SWFI, sterile water for injection.

TABLE 3.

Practical Considerations for Poly-L-Lactic Acid Injection

- The viscosity of PLLA is very low compared with hyaluronic acid gel; therefore, caution should be exercised to avoid inadvertent overcorrection.
- A 25-gauge, 1.5-inch needle is recommended for PLLA injection; the syringe needle should be primed prior to injection.
  - o A 22-gauge, 50-mm cannula may also be considered.
- Excessive foam in the syringe may lead to needle clogging; this may be addressed by removing the needle from the syringe and pushing the plunger until the foam is expelled through the syringe hub. A new needle can then be attached.
- Any product remaining after a patient's session should be discarded.

PLLA, poly-L-lactic acid.

- The authors have achieved optimal results in the following areas:
    - Temporal fossa
    - Malar/submalar areas
    - Chin and mandible
    - Décolletage
- Potentially problematic areas include:
    - Areas of hyperdynamic muscle movement (eg, perioral and periocular regions)
        - This may lead to microparticle clumping, localized overcorrection, and nodules/papules.
    - Neck and hands
        - The thin skin in these areas requires superficial injections, increasing the possibility of nodule and papule formation.

Injection Techniques

Favorable injection techniques allow slow, safe, uniform dispersion of PLLA at the proper depth for optimal cosmetic benefit.

General considerations include:

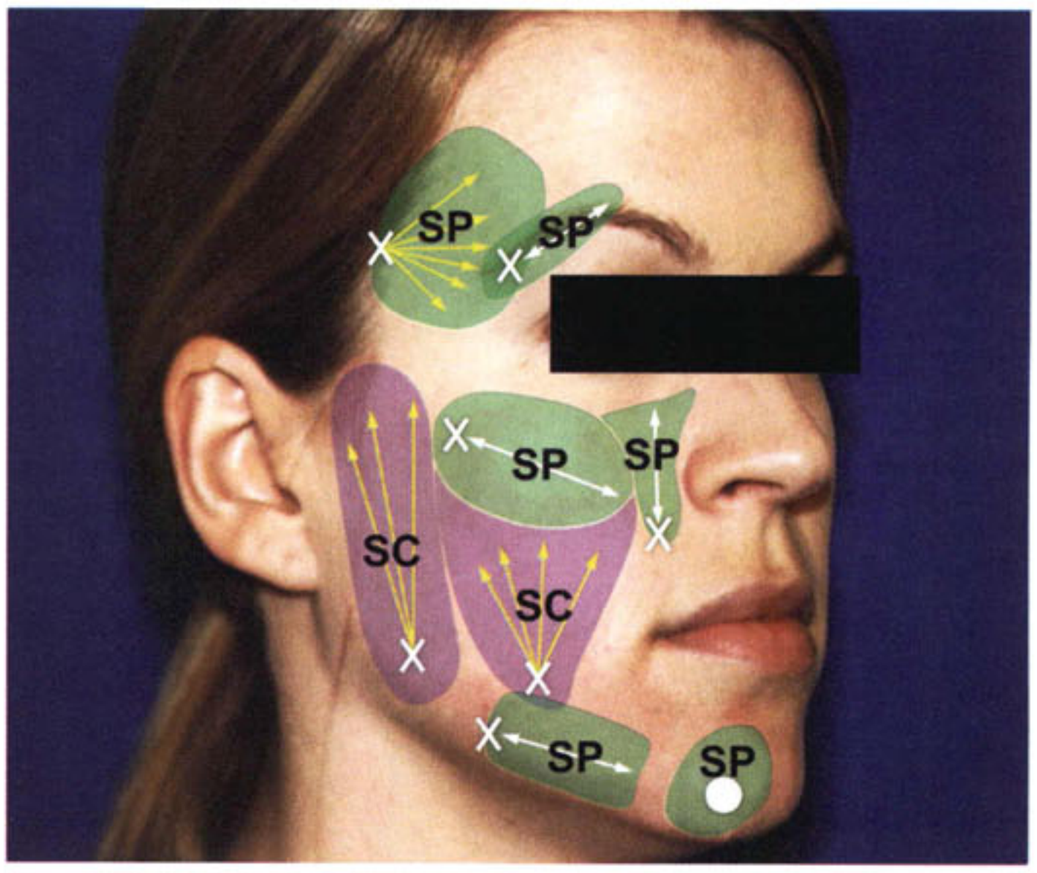
- Injection should be into the subcutaneous or supraperiosteal plane.
    - Superficial injection (ie, into the dermis) should be avoided, as this may lead to visible neocollagenesis.
- A reflux maneuver should be performed routinely to eliminate any risk of inadvertent intravascular injection.
- Injection should be performed slowly.
- If the needle clogs, it should be removed and the foam pushed out of the syringe hub. A new needle should then be affixed and primed prior to injection.
- Injection technique can generally be selected based on the experience and comfort level of the clinician, with consideration given to the anatomic area being treated (see below).
    - A cross-hatch pattern should be considered, especially while becoming familiar with PLLA.
    - With more experience, fanning, cross-fanning, and depot approaches are also commonly utilized.
        - Fanning has the advantage of fewer needle sticks; however, vigilance is required to avoid multiple deposits at the apex of the fan.

Site-specific recommendations on the injection of PLLA for facial soft tissue augmentation include (Figure 1)[34]:

- Medial cheek/Mid-face
    - Inject supraperiosteally over the zygoma, maxilla, and canine fossa/pyriform aperture.
    - Injectinto the deep subcutaneous plane in the submalar/mid-cheek, where bony background is absent.
- Lateral face
    - Inject in the superficial subcutaneous fat above the parotid gland and masseter muscle.

FIGURE 1. Site-specific recommendations for the injection of poly-L-lactic acid (PLLA).[34]

- Potential areas amenable to correction with PLLA are indicated on this model. Recommended points of entry for each anatomic site are marked with a white X.
- Injectable PLLA should be placed supraperiosteally in the temples, lateral brow, zygomatic area, maxillary area, mandibular area, and mental area (green areas marked with "SP").
- Injectable PLLA should be placed in the subcutaneous fat in the mid-cheek regions and preauricular area (purple areas marked with "SC").
- Depending on the anatomic area, recommended techniques include fanning (yellow arrows), retrograde linear threading (white arrows), or depot (white circle) injection.



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- Mandible/Chin
    - Inject supraperiosteally over the menton, pre-jowl sulcus, and antegonial notch
- Temporal fossa/Lateral brow
    - Inject supraperiosteally at the origin of the temporal muscle.
    - Inject supraperiosteally at the tail of the brow.
- Periorbital supraperiosteal injections approached through the orbicularis oculi muscle should be avoided.
    - This approach may lead to papule formation, perhaps resulting from extrusion of PLLA along the needle tract during muscular contraction.

Injection Quantity and Frequency

- The amount of surface area to be treated is the sole determinant of the amount of PLLA used during a session.
    - The vast majority (~98%) of patients should receive 1-2 vials per session if treating the whole face (0.5–1 vial per side).
        - Up to 3 vials may be required for a patient requiring treatment over a very large surface area.

- A uniform distribution of product should be ensured for each treated region (ie, coat the region); injection should not vary by particular focal areas or based on specific cosmetic deficits.
- The final volumetric correction is determined by the number of treatment sessions.
- Treatment can continue until the patient is satisfied with the results.
    - Most experts find 3–5 sessions to be optimal.
    - Younger or fuller faces need less product and fewer sessions.
- An interval of at least 4 weeks between sessions is recommended.
- Subsequent courses of treatment (ie, "top-up" courses) typically occur 2 years after the initial course.
    - During these courses, less PLLA per session, and a fewer number of sessions, are generally required.
    - Some patients prefer once-a-year, single-session maintenance treatments to keep pace with the aging process.

Post-treatment Massage

- Although data to support post-treatment massage are limited, massaging the injected area for a few minutes after treatment is recommended.
- Continued self-massage by patients may be left to the discretion of the treating physician.

"As clinical experience has grown, we have come to better understand the technical and mechanistic aspects of poly-L-lactic acid use that need to be considered to optimize patient outcomes."

SUMMARY

These recommendations are consistent with the authors' perspectives on "best practices" with the use of PLLA for soft tissue augmentation. It is our hope that these recommendations will both increase clinicians' confidence in the use of this agent and lead to predictable, consistent, and favorable outcomes across the range of patients seeking cosmetic enhancement.

Facial Volumization With Poly-L-Lactic Acid: Representative Results

Due to an increasing societal emphasis on the importance of a youthful appearance, as well as the development of new treatment options, there is a rising consumer demand for procedures that can reverse the signs of aging. For many patients with facial volume loss, poly-L-lactic acid (PLLA) is an excellent treatment choice. Its mechanism of action results in cosmetic effects that have a gradual onset and last 2 years or more, which is well-matched with reported patient preference for durable benefits. Refined PLLA methodology, along with a better understanding of the structures in the aging face and how they interrelate, now allows for favorable and predictable results across a range of patient types.[31]

In the above consensus recommendations, we detail procedures for the proper administration and aftercare of PLLA including: careful patient selection and education, proper preparation and storage, optimal injection techniques, and after-injection massage. Here, we provide some representative before-and-after photographs of several of our patients, which illustrate how the implementation of these recommendations during PLLA soft tissue augmentation can replace lost facial volume and sustain this restoration.

Figure 2 shows a 34-year-old patient before and after her PLLA therapy, with injected areas indicated. Figure 3 demonstrates the progression of PLLA enhancement in a 38-year-old female patient at 6 months and 1 year after beginning therapy. In Figure 4, a 30-year-old female patient is shown at baseline, 2 months, and 2 years after PLLA therapy was initiated. In this patient, PLLA was injected in the supraperiosteal space to enhance the jaw line.

FIGURE 2. Thirty-four-year-old female patient with early signs of facial volume loss. The image on the left **a)** shows the patient prior to beginning poly-L-lactic acid (PLLA) therapy. The image on the right **b)** was taken 5 months after the initial PLLA injection session. One vial of PLLA was injected monthly at 3 sessions (3 vials total). Injection areas included the temple, cheek, preauricular area, pyriform fossa, and marionette line/chin area. Photographs courtesy of Melanie D. Palm MD MBA.

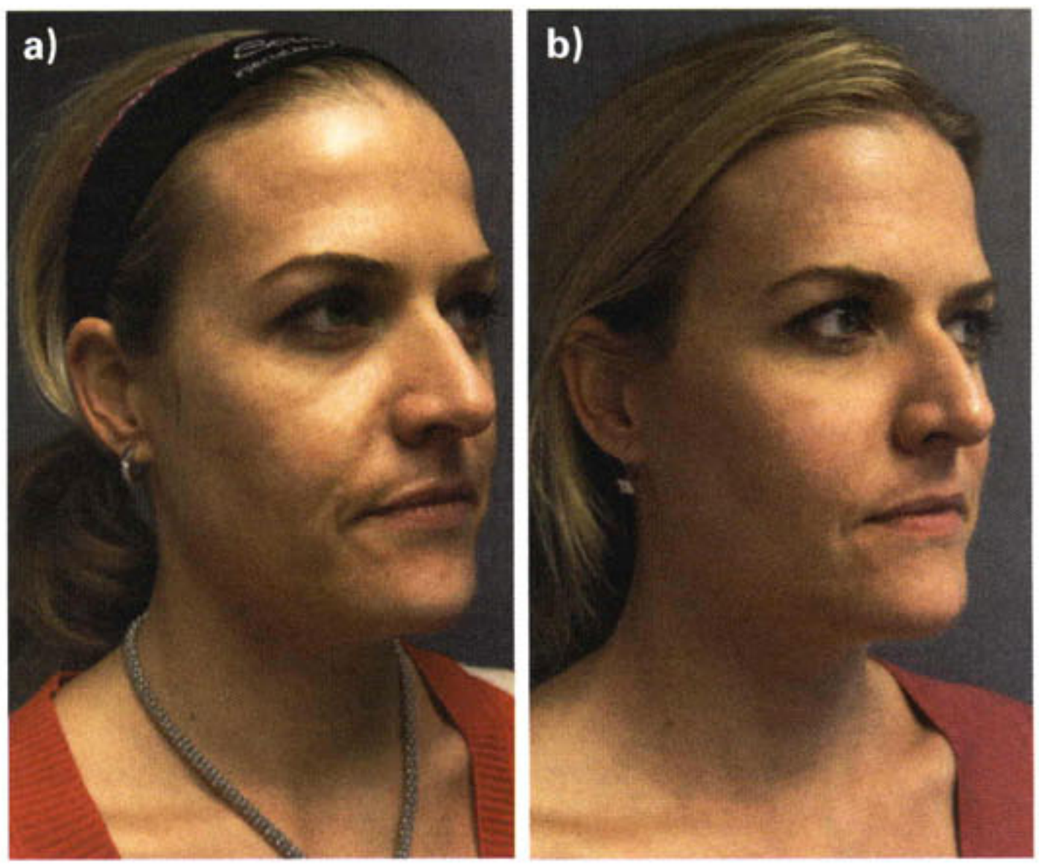


FIGURE 3. The progression of the restoration of facial volume loss and correction of facial asymmetry with poly-L-lactic acid (PLLA) injections in a 38-year-old female patient. This patient had 3 sessions of PLLA injections, 2 vials per session, spaced 1 month apart. The first photograph **a)** shows the patient before the administration of PLLA, and the "after" photographs show the results at **b)** 6 months and **c)** 1 year after beginning therapy. Photographs courtesy of Rebecca Fitzgerald MD.

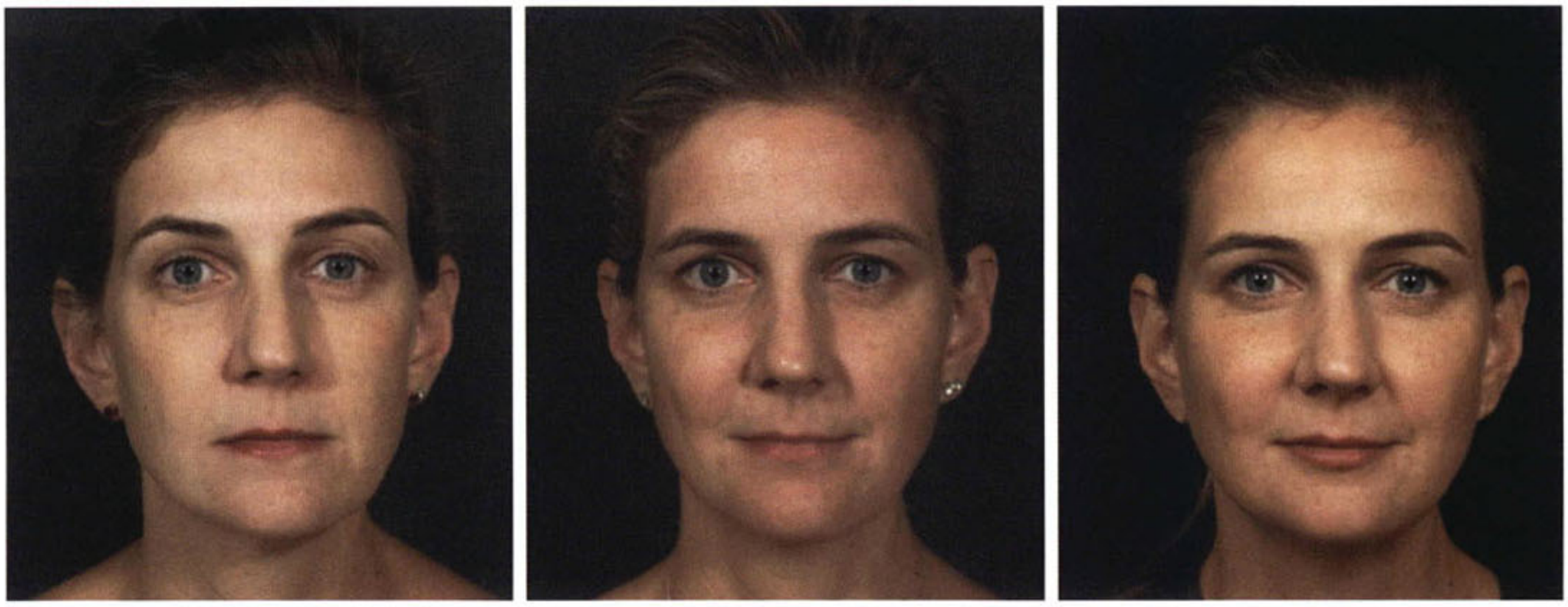
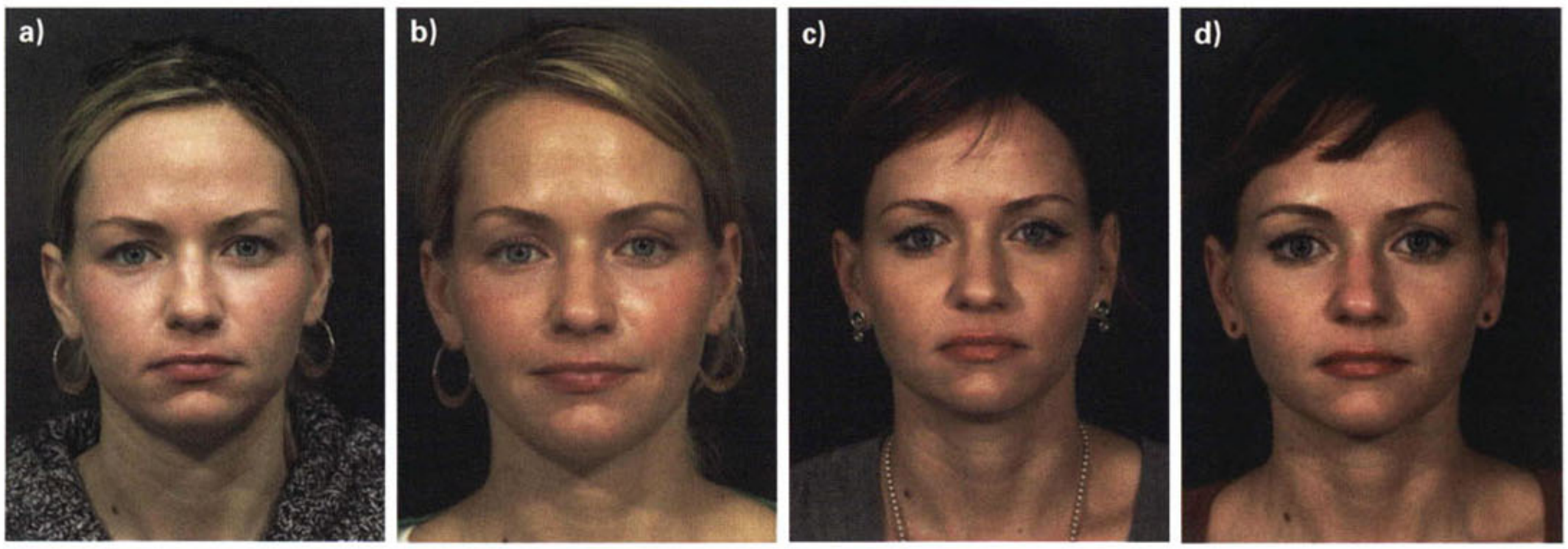


FIGURE 4. These are photographs of a 30-year-old female patient treated with poly-L-lactic acid (PLLA), 2 vials/session, 2 sessions spaced 1 month apart over a period of 29 months. **a)** Baseline; **b)** 3 months after treatment was initiated; **c)** 27 months after initial treatment; and **d)** 1 month following touch-up with 1 vial of PLLA. The patient received no other treatment. Note the brow elevation and change in the perioral area with supraperiosteal injections along the supraorbital rim, zygoma, maxilla, and mandible. Photographs courtesy of Rebecca Fitzgerald MD.



DISCLOSURES

Danny Vleggaar MD has been a medical consultant for Sinclair IS Pharma, France; PharmaSwiss SA, Switzerland; Valeant Eastern Europe; and Cutanea Life Sciences, Inc. He also has been a trainer for Valeant Pharmaceuticals International, Inc./Medicis Corporation.

Rebecca Fitzgerald MD has been a consultant and speaker for Valeant Pharmaceuticals North America LLC/Medicis Corporation; Merz Aesthetic, Inc; and Allergan USA, Inc.

Z. Paul Lorenc MD FACS has been a consultant for Johnson & Johnson; La Lumiere, LLC; Medicis Corporation; Merz Corporation; and Mentor Corporation. In addition, he holds the following patents: US Patent 5/611,814–Resorbable Surgical Appliance for Use in Supporting Soft Tissue in a Superior Position; US Patent 60/950,423–Composition and Method of Use for SoftTissue Augmentation/Drug Delivery; US Patent 12/797,710–Method for Measuring Change in Lip Size After Augmentation; and US Patent 13/604,012–Light Therapy Platform System.

J. Todd Andrews MD has been a medical consultant for Sinclair IS Pharma, France. He has also been a consultant and trainer for Valeant Pharmaceuticals North America LLC/ Medicis Corporation, and Allergan USA, Inc.

Kimberly J. Butterwick MD has served as an Advisory Board member for Allergan, Inc. and has received honoraria as a consultant for Allergan, Inc., Merz Corporation, and Valeant Pharmaceuticals International, Inc.

Jody A. Comstock, MD has been a physician trainer, speaker, and consultant for Allergan, Inc., Lumenis, and Valeant Pharmaceuticals International, Inc. He has also been a speaker and consultant for Obagi Medical Products, Inc., a division of Valeant Pharmaceuticals North America LLC and SkinCeuticals International.

C. William Hanke MD has served as a consultant for and has received clinical research grants from Valeant Pharmaceuticals International, Inc. to conduct studies on poly-L-lactic acid.

T. Gerald O'Daniel MD FACS serves as a physician trainer for Sculptra for Valeant Pharmaceuticals International, Inc.; he receives no support or financial assistance. He has no other relationships to disclose.

Melanie D. Palm MD MBA has served as a physician trainer, speaker, and consultant for Valeant Pharmaceuticals.

Wendy E. Roberts MD has served as a consultant, speaker, and Advisory Board member for and has received honoraria from: Allergan Medical, Allergan Cosmetic, Kythera Biopharmaceuticals, La Roche-Posay, L'Oréal, MELA Sciences, NeoStrata Company, SkinMedica, Top MD, Theraplex, and Valeant Pharmaceuticals International, Inc.

Neil Sadick MD has received research grants from Allergan, Inc. and Valeant Pharmaceuticals North America LLC, and is a member of the Advisory Board for Merz Pharmaceuticals and Valeant Pharmaceuticals North America LLC.

Craig F. Teller MD has conducted research for Allergan, Inc. and Amgen Inc., and has received consultant honoraria from and served as a member of the Advisory Board and/or Speakers' Bureau for AbbVie Inc., Allergan, Inc., Amgen Inc., Celgene Corporation, Merz Corporation, Taro Pharmaceuticals U.S.A., Inc., and Valeant Pharmaceuticals International, Inc./Medicis Corporation.

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stimulate neocollagenesis from fibroblasts, leading to volume correction. The PLLA microspheres themselves are gradually degraded and do not directly contribute to the final result. Three to 4 sessions every 4 to 6 weeks are needed to achieve optimal correction, which can last 18 to 25 months.[2–5] Most providers use PLLA to correct panfacial volume loss.[2,3]

Because PLLA stimulates neocollagenesis, it is possible it may also be beneficial in the treatment of lax skin of the knee. In this study, the efficacy, safety, and patient satisfaction of the treatment of knee skin laxity and crepiness with PLLA will be evaluated.

Materials and Methods

Study Design

This is a randomized, double-blinded, split-body, placebo-controlled study. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in approval by the institutional review board. Twenty female subjects between the ages of 30 and 65 years with symmetric, bilateral, mild to severe upper knee laxity on the upper knee laxity/crepiness grading scale (see **Supplemental Digital Content 1**, Figure S1, http://links.lww.com/DSS/A474) were enrolled. Subjects must have had a stable body weight for at least 6 months before study entry. Subjects were excluded if they had undergone any skin tightening treatments in the past 12 months, ever received biostimulatory/filler injections, or undergone nonablative laser treatments in the past 3 months in the treatment area. They were also excluded if they had a history of hypertrophic or keloidal scarring.

Active and Placebo Treatments

Each subject's knees were randomized to receive 3 treatments of PLLA 4 weeks apart in 1 knee, whereas the other knee received 3 treatments of bacteriostatic water and served as the control. The active side received 1 vial of PLLA diluted with 14 mL of bacteriostatic water and 2 mL of 1% plain lidocaine. The control side received 16 mL of bacteriostatic water. The treatment area was limited to the skin of the anterior upper knee. Injections were not placed lower than the superior border of the patella. The area treated was 10 cm in height (superior–inferior plane) and 10 cm in width (medial–lateral plane). The active and placebo product was injected with a 25 gauge, 1 ½ inch needle using a retrograde fanning technique. After the treatment session, patients massaged both knees for 5 minutes, 5 times per day, for 5 days.

Evaluation of Efficacy, Safety, and Satisfaction

Primary endpoints included the blinded investigator laxity/crepiness grading scale, the Physician Global Aesthetic Improvement Scale (PGAIS) by a blinded evaluator, and the blinded evaluator identification of the treated knee. The blinded investigator laxity/crepiness grading scale was performed at postfinal treatment days 28, 84, and 168. The PGAIS (see **Supplemental Digital Content 2**, Figure S2, http://links.lww.com/DSS/A475) was performed after treatment 3 and postfinal treatment days 28, 84, and 168. The blinded evaluator (by a different evaluator who did not perform the treatments) identification of the treated knee was performed after all subjects had completed the study.

Secondary endpoints included the Subject Global Aesthetic Improvement Scale (SGAIS) and the subject satisfaction questionnaire. Both these assessments were completed after treatment 3 and postfinal treatment days 28, 84, and 168. The treating physician also evaluated for side effects (erythema, edema, contour abnormality, and nodules) after every treatment and at postfinal treatment days 28, 84, and 168.

Photographic Documentation

Before each treatment and at the postfinal treatment days 28, 84, and 168 visits, standard 2D photographs were taken, capturing 3 views: anterior, right oblique (45°) and left oblique (45°). Vectra 3-D photography was also performed at these visits. The subjects were standing during all photographs.

Statistical Analysis

Statistical evaluation was performed with Microsoft Excel 2013. The 2-tailed Student *t*-test was used to determine the difference in means between groups. All data are represented as mean ± SD.

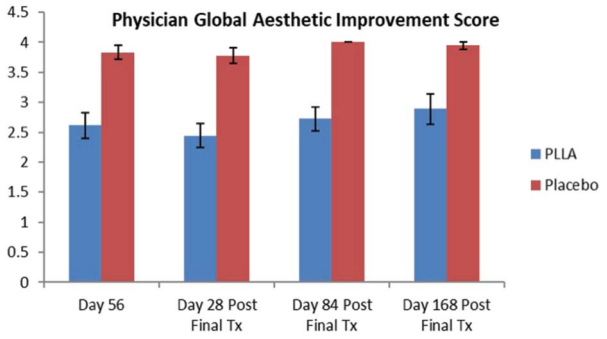

Figure 1. Physician Global Aesthetic Improvement Scale scores at Day 28, Day 84, and Day 168 after final treatment. All *p* values were <0.05. PLLA, poly-L-lactic acid.

Results

Subject Demographics

Twenty subjects were enrolled in the study. The mean subject age was 56.2 years (range 48.2–65.5 years of age). Eighteen patients completed the study, and 2 patients were lost to follow-up.

Efficacy

Statistically significant improvement as rated on the PGAIS was seen at Day 28 after final treatment ($p < 0.05$) in the active knee when compared with the placebo knee. This improvement was sustained at the Day 84 ($p < 0.05$) and Day 168 ($p < 0.05$) after final treatment visits (Figure 1). At Day 168 after final treatment, the mean PGAIS was 2.89 (1 = very much improved, 2 = much improved, 3 = improved, 4 = no change, and 5 = worse) in the active knee versus 3.94 in the placebo knee. At Day 84 after final treatment, 16 of 18 patients (89%) and 0 of 18 patients were noted to have improvement in their active and placebo knees, respectively. Of these 16 active knees with improvement, 2 were noted to be "very much improved," 3 were noted to be "much improved," and 11 were noted to be "improved." At Day 168 after final treatment, 12 of 18 (67%) patients and 1 of 18 (6%) patients were noted to have improvement in their active and placebo knees, respectively. A representative set of images can be seen in Figures 2.

No statistically significant difference in the blinded investigator laxity/crepiness scale was detected between the active and placebo knees at the days 56, 84, and 168 after final treatment visits (Figure 3). No statistically significant difference was seen between the active and placebo knees on the subject global aesthetic score or the subject satisfaction scale (Figures 4 and 5).

Blinded investigator assessments at the end of the study involved comparison of pretreatment and Day 168 after final treatment photographs. The blinded investigator was able to identify the post-treatment photograph in 5 of 18 patients and the active knee in 7 of 18 patients.

Safety and Tolerability

Poly-L-lactic acid treatments were well tolerated without any significant adverse events. Physician assessments of erythema, edema, contour irregularity, and nodules revealed no statistically significant difference between the active and placebo groups. There were no cases of edema, contour irregularity, or nodules in either the active or placebo knees. Mild erythema was noted in both the active and placebo knees in 6 of the patients at the Day 56 after the final treatment visit and had resolved in both knees at the Day 84 after the final treatment visit.

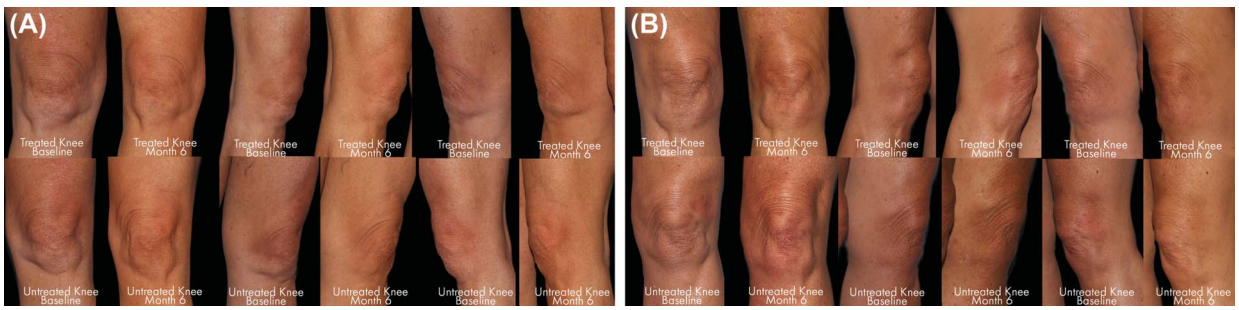

Figure 2. Patients (A and B): Treated (top) and untreated knee (bottom) at baseline and 6 months after final treatment from different angles.

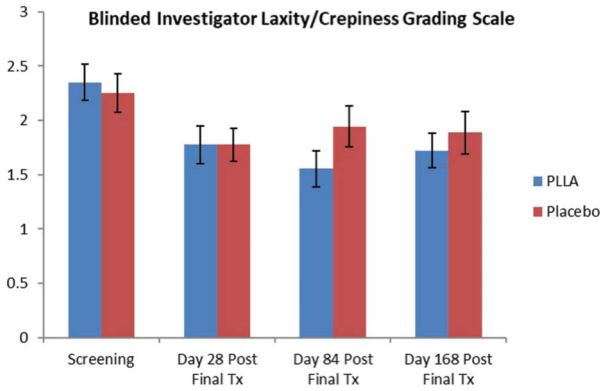

Figure 3. Blinded investigator laxity/crepiness scale at Day 28, Day 84, and Day 168 after final treatment. PLLA, poly-L-lactic acid.

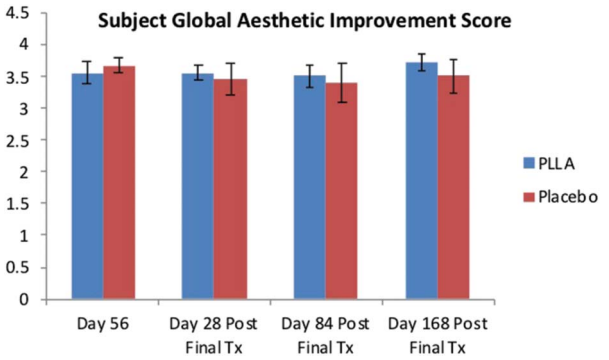

Figure 4. Subject Global Aesthetic Improvement Scale scores at Day 56 (56 days after first PLLA treatment) and Day 28, Day 84, and day 168 after final PLLA treatment. PLLA, poly-L-lactic acid.

Discussion

Given the rise of off-face skin tightening in the last decade, upper knee laxity has become a common concern among patients. Liposuction does not address laxity, and surgical removal of excess skin ("thigh lift") is an invasive procedure which does not adequately address knee laxity, and results in scars and possible adverse events. Resurfacing is also not an option given the paucity of sebaceous glands in this cosmetic unit.

Over the last decade, off the face application of PLLA has become more popular, and it has been used for chest wrinkles, buttock augmentation, and for crepiness of the arms.[6–9] This is the first study to assess the efficacy and safety of PLLA in the treatment of upper knee laxity. Based on our study, PLLA seems to be a safe and effective modality in addressing upper knee skin laxity. Significant improvement in the PGAIS was noted at Day 28 after final treatment, and this improvement was sustained at 84 and 168 days after final treatment. Specifically, 89% of subjects versus 0% of subjects were noted to have improvement in their active and placebo knees, respectively, at the Day 84 after the final treatment visit. Investigators continued to note a difference at the Day 168 after the final treatment visit as 67% (12 of 18) of subjects were noted to have improvement in the active knee versus only 6% (1 of 18) had improvement in the placebo knee. Poly-L-lactic acid treatments were also well tolerated without any incidence of nodules.

No statistically significant improvement was seen in the blinded investigator laxity/crepiness scales. This scale is not validated and therefore may not have been as sensitive to consistently and reliably capture improvement in skin quality and tightening. In addition, there were statistically significant changes in the SGAIS or subject satisfaction scores between the active and placebo knees. Lack of statistically significant outcomes in these measures may be due to the limited follow-up period of 6 months. Recent research has demonstrated that PLLA enhances skin quality in a time-dependent manner and that significant improvement in skin quality (specifically radiance, pore size, pigmentation, and smoothness) may not be seen until 12 months after the final treatment.[10] Thus as the follow-up period in this study was only 6 months, further improvement in laxity that may have occurred at 12 months was not captured.

Figure 5. Subject satisfaction scale scores at Day 168 after final treatment. PLLA, poly-L-lactic acid.

The limitations of this study include its small sample size, limited follow-up period of 6 months, and that it was conducted at a single center. A larger sample size may have allowed for clearer conclusions to be drawn regarding efficacy. Furthermore, a larger sample size would have allowed for detection of more subtle changes in the outcome measures. Finally, using a validated skin quality scale may have helped to detect nuanced changes in skin quality.

Poly-L-lactic acid may be an effective and safe non-invasive modality for treating laxity and improving the appearance of the upper knee. As microfocused ultrasound has also been shown to improve upper knee laxity, PLLA may be combined with microfocused ultrasound to enhance the improvement in upper knee laxity.[1] Combination laser/light treatments and injectables have become increasingly popular in the last decade because of the synergistic potential when certain treatments are paired together. Given the inconsistent results in this study, further studies with a larger sample size, longer follow-up period, a validated knee laxity scale, and combination therapy with microfocused ultrasound therapy can delineate the optimal therapeutic regimen to treat upper knee laxity.

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