High-Dilution Technique With Injectable Poly-L-lactic Acid

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When using poly-L-lactic acid (PLLA) as an injectable device, undesired effects, most commonly subcutaneous papules, may occur and are thought to result from technique variations. To improve patient satisfaction, techniques must be developed to minimize adverse and undesirable effects. We sought to describe finite techniques that may minimize the occurrence of subcutaneous nodules, specifically through the technique of high-volume dilution. In total, 10 participants (3 men and 7 women) aged 51 to 65 years were injected using the high-dilution technique, with dilution of PLLA within 8 mL of solution rather than 5 mL of sterile water and lidocaine. In addition to the nasolabial folds, we involved off-label injection sites at the mandible, cheeks, upper zygoma, and temporal region to assess for versatility. Three participants (30%) reported the expected side effects of bruising and swelling immediately postinjection, with complete resolution within 5 to 14 days. The same 3 participants (30%) reported erythema immediately postinjection as well. There were no reports of inflammation or edema 1 to 14 days postinjection. Of the 10 participants now followed for more than 24 to 40 months, 1 (10%) developed a nonvisible papule on the midcheek. At the time of follow-up, all 10 participants reported being "very satisfied" given the options of: very satisfied, satisfied, neutral, or unsatisfied.

Injectable devices are used in cosmetic procedures for facial rejuvenation and restoration of volume loss. Soft tissue fillers like poly-L-lactic acid (PLLA) are excellent candidates for the treatment of concavities caused by the aging process. Poly-L-lactic acid in the form of Sculptra (Dermik Laboratories, sanofi-aventis), was approved by the US Food and Drug Administration in August 2004 for the treatment of human immunodeficiency virus (HIV)-associated lipoatrophy. More recently, in July 2009, the US Food and Drug Administration approved Sculptra Aesthetic for the correction of shallow to deep nasolabial folds, contour deficiencies, and facial wrinkles. Unlike static fillers that produce the desired outcome primarily through mass effect, PLLA stimulates endogenous collagen production by fibroblasts to generate new volume through eliciting a foreign-body response.[1] This provides an effect that can last for many years.[2]

The efficacy and safety of PLLA as an injectable device have been well established.[1] However, undesired effects, most commonly subcutaneous papules, may occur and are thought to result from technique variations in reconstitution, product distribution in the suspension, depth of injection, or poor posttreatment management or massage. Original studies show rates of PLLA injection-site subcutaneous papule formation ranging from as high as 31% to 52%.[3,4] Other adverse effects from the original

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Dr. Marmur is a trainer for sanofi-aventis. Drs. Henry and Mohammad have no conflicts of interest relevant to this article.

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studies include swelling, erythema, and bruising. A new study reflecting these adverse effects displays rates of 81%, 77.6%, and 64.7%, respectively.[5] Although studies have examined the cosmetic outcome in both HIV and non-HIV patients treated with PLLA, few investigations have been done to examine techniques to minimize adverse effects. Therefore, we sought to describe finite techniques that may minimize the occurrence of subcutaneous nodules, specifically through the technique of high-volume dilution.

METHODS

The purpose of this study is to describe new techniques for injection and assess whether there is a decrease in the aforementioned adverse effects following dilution of PLLA within 8 mL of solution rather than 5 mL of sterile water and lidocaine.

In total, 10 participants (3 men and 7 women) aged 51 to 65 years were enrolled in the study. All participants indicated a desire to restore volume in the face. In addition, male participants wanted to maintain a masculine posterior mandibular angle, and female participants expressed a desire to restore upper facial volume (temples, cheekbones), a triangular jawline, and elongation of the chin.

Procedure

Prior to injection, participants were informed of the risks and benefits and signed the appropriate documents. Facial analysis and mapping was done by the treating physician. Standardized pretreatment photographs of the face (frontal and oblique views) were taken before the initial injection. To assess improvement following injection, postinjection photographs were taken. Depending on the participant, 1 to 4 vials were used per treatment. In addition, each participant received 1 to 4 treatments.

The PLLA vial was reconstituted 24 hours prior to the procedure without vigorous shaking within an 8-mL solution consisting of 5-mL bacteriostatic, sterile water in addition to 3-mL lidocaine containing epinephrine 1% immediately preprocedure. Next, a 20-gauge needle was inserted into the PLLA vial, and the product was pulled into a 1-mL syringe. The syringe was slowly pulled up and down 5 times, and then filled to 1 mL. The syringe was then disengaged from the 20-gauge needle, which remained in the vial. The plunger in the syringe was immediately pulled back to introduce air into the neck or hub of the syringe, just enough so that there was no product in that narrow space to prevent clogging. A 26-gauge needle with a length of half to 1 inch was then attached to the syringe. Nine participants received 2 vials of PLLA, and one participant received 1 vial of PLLA. No participant received a portion of a vial; however, had a portion of a vial been used, the syringe would have been changed after each withdrawal from the vial to prevent cross-contamination.

During injection sessions, clogging of the syringe may occur. Do not express product while the needle remains in the tissue by using extra force because of the risk of a bolus injection. Remove the needle, pull back slightly on the handle, and express quickly. If clogging occurs, it may be due to foam formation if the vial has been vigorously shaken.[6] The foam can be removed by removing the needle and pushing it past the hub of the syringe. If foam is not forming but clogging occurs consistently, contact the manufacturer to record the lot number. If necessary, change the needle or change the syringe.

Two basic techniques are used when injecting PLLA: a tunneling technique and a depot technique. Both techniques have been detailed by expert PLLA injectors.[1,6] The tunneling crosshatch technique was used in the lower facial region, more specifically in the cheeks and nasolabial folds, whereas the depot technique was used in the upper zygoma and temporal areas. The tunneling technique is done with a 26-gauge needle. The needle is introduced at a 30- to 40-degree angle until the subcutaneous junction is reached. Countertraction with the nondominant hand is used to control the injection depth. When the subcutaneous plane is reached, the needle angle is lowered to advance within the plane. The reflux maneuver of injection is done to avoid intravascular injection. A thin thread of PLLA is injected into the tissue plane as a retrograde injection. The total volume should be limited to 0.1 to 0.2 mL per injection. Deposition in the superficial skin is avoided by stopping before the needle bevel is visible in the skin. If the needle is too superficial, the skin appears to dimple with movement of the needle. If dimpling is seen, retract the needle to the entry point while keeping the needle tip in the dermis; then reposition the needle, aiming at a deeper plane. Advance the needle for placement while watching for dimpling. If no dimpling occurs, begin the retrograde threading at an even pace. Stop injecting product while the needle tip is still in the desired subcutaneous plane, not while withdrawing the needle tip through the dermis. The product tracts back with the needle tip in the path of least resistance toward the point of entry. This increases the risk of superficial product and an undesired effect. Using this technique, repeated small threads were injected in a gridlike manner of parallel and perpendicular lines into the deep dermis to create a crosshatch pattern.

According to some injectors,[6] the depot technique generally requires less product to attain the desired

result. The technique involves injecting small aliquots of approximately 0.1 to 0.2 mL (according to the package insert)[7] at a deep supraperiosteal level. Recent recommendations from experienced injectors of PLLA suggest 0.3 to 0.5 mL per depot injection.[6] The depot technique used along the mandible may also be used in other areas such as the temples. Injections were done along the mandible and chin (as also described by other authors) by inserting the needle after lifting the lip depressor muscles away from the bone, followed by firm massage.[6] Continue to massage each injection area while preparing the next 1-mL syringe. Do not prefill all syringes because of the risk of separation of solute and diluent. Each session may be accomplished with one syringe and several needles (replacing with every new area to ensure a sharp, less painful needle.)

Injection around the eyes was avoided as the orbicularis oculi is a hyperkinetic muscle that may lead to clumping of the product and, hence, formation of nodules. Injectable hyaluronic acid is preferred underneath the eyes. Injection of PLLA in the lips should also be avoided for the aforementioned reasons.

Postinjection, participants were educated on self-massage and instructed to massage the injection site to optimize results and minimize adverse effects. In addition, they were directed to the product's official Web site for additional information and expectations during their postoperative course. In the authors' experience, patient compliance with vigorous massage of all treated areas is essential to success. The recommendation is 5 minutes of massage 5 times a day for 5 days. The patients receive written instructions for postprocedural care and often receive a telephone reminder the day after.

RESULTS

Three participants (30%) reported the expected side effects of bruising and swelling immediately postinjection, with complete resolution within 5 to 14 days. The same 3 participants (30%) reported erythema immediately postinjection as well. There were 0 reports of inflammation or edema 1 to 14 days postinjection.

This result can be compared to that of a newly published study,[5] which reflects a rate of 81% for localized swelling, with 35% of those participants experiencing swelling for 2 to 7 days and only 2% for 8 to 14 days. That same study displayed localized bruising in 64.7%, with a duration of 2 to 7 days in 44% of those participants and 8 to 14 days in 7%, as well as localized erythema in 77.6% of the participants, with 50% of those participants experiencing erythema for 1 to 24 hours and 24% for 2 to 7 days.[5]

Following each injection, participants were seen every 6 weeks during the injection series. Each follow-up session included a satisfaction assessment suvey, and additional photographs were taken. Of the 10 participants now followed for more than 24 to 40 months, 1 (10%) developed a nonvisible papule on the midcheek. A prior published study reflects a papule formation rate as high as 44%.[3] At the time of follow-up, all 10 participants reported being "very satisfied" with the outcome when given the options of very satisfied, satisfied, neutral, or unsatisfied.

All 10 participants displayed high rates of compliance with postoperative instructions, which included massage at the injection site. At follow-up visits, the participants requested fractional laser resurfacing and botulinum toxin injections, underscoring that patient satisfaction leads to ideal combination therapy in cosmetic surgery.

COMMENT

Facial aging is a 3-dimensional process. Rohrich and Pessa[8] elegantly stated that "the subcutaneous fat of the face is partitioned into discrete anatomic compartments. Facial aging is, in part, characterized by how these compartments change with age." In a subsequent publication, Rohrich et al[9] stated that "volume loss of specific deep fat compartments leads to predictable changes in the topography of the face." Each compartment ages independently, requiring individualized treatment for every patient (Figure 1). Through 3-dimensional imaging, Lambros[10] showed that the youthful face has ample volume, which displays a smooth transition from one area to the other. The goal of volume repletion is to restore this seamless transition between facial compartments. Poly-L-lactic acid is a reliable and appropriate filler for long-term results in these deep compartments. Furthermore, a recent study by Fitzgerald and Vleggaar[6] illustrates the versatility of PLLA use in mimicking volume in multiple tissue layers to create a more naturally youthful appearance. It is this versatility, in addition to its biocompatibility, that has increased demand for tissue augmentation with PLLA.

To meet this demand and maintain patient satisfaction, it is important that physicians develop techniques to minimize adverse side effects. In our experience, as with that of others, the most commonly observed adverse event associated with PLLA is the delayed occurrence of subcutaneous papules confined to the injection site. These are typically palpable, asymptomatic, and nonvisible.[11] At times, these papules are difficult to treat, not responding to interlesional corticosteroids even at doses that induce facial atrophy.[12] A review of the PLLA literature reveals a sometimes contradictory delineation

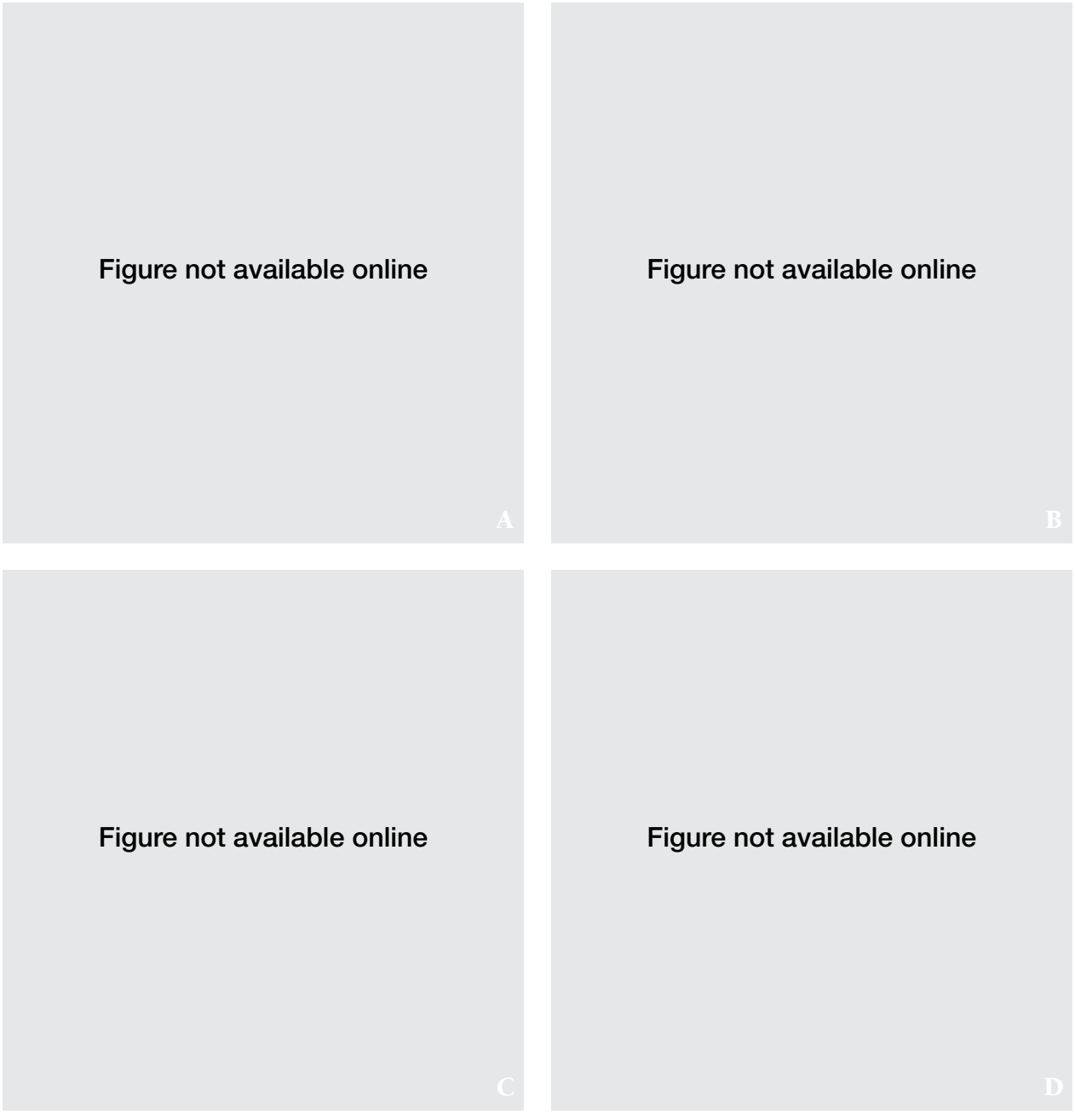
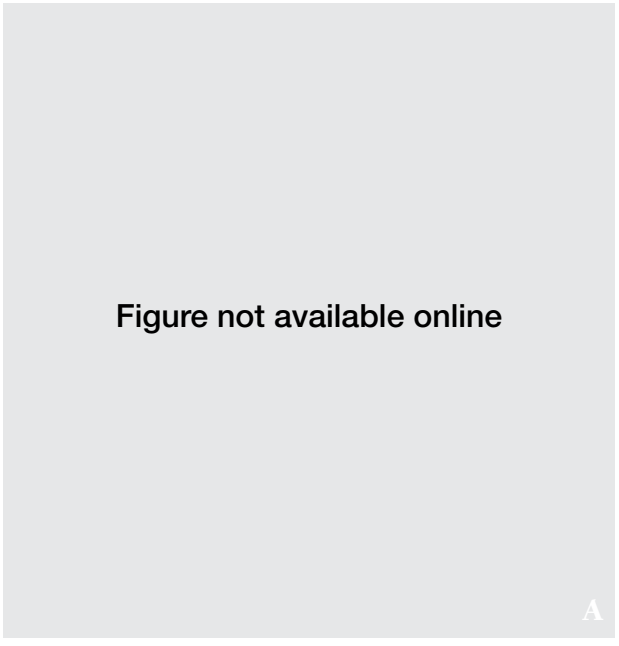


Figure 1. Frontal view before poly-L-lactic acid (PLLA) augmentation (A). Profile before PLLA augmentation (B). Frontal view after PLLA showing improvement in nasolabial folds, upper zygoma, and mandible (C). Profile view after PLLA showing improvement in nasolabial folds, upper zygoma, and mandible (D).

between papules, nodules, and granulomas.[13] Hamilton et al[11] categorized nodules into early-onset and late-onset nodules. Early-onset nodules occur 1 to 3 months after injection, are 1 to 2 mm in size, gradually appear, and are poorly responsive to intralesional corticosteroids. Late-onset nodules are more rare and abruptly appear with edema and dyspigmentation 6 to 36 months after injection. According to Hamilton et al[11] late-onset nodules typically respond well to intralesional corticosteroids. Late-onset papules may fit the criteria of what other authors describe as granulomas and would need to be biopsied and confirmed histologically.[13] We investigated the formation of early-onset nodules in our participants and believe that highly concentrated product may lead to clumping and nodule formation that may be remedied by high dilution of the product.



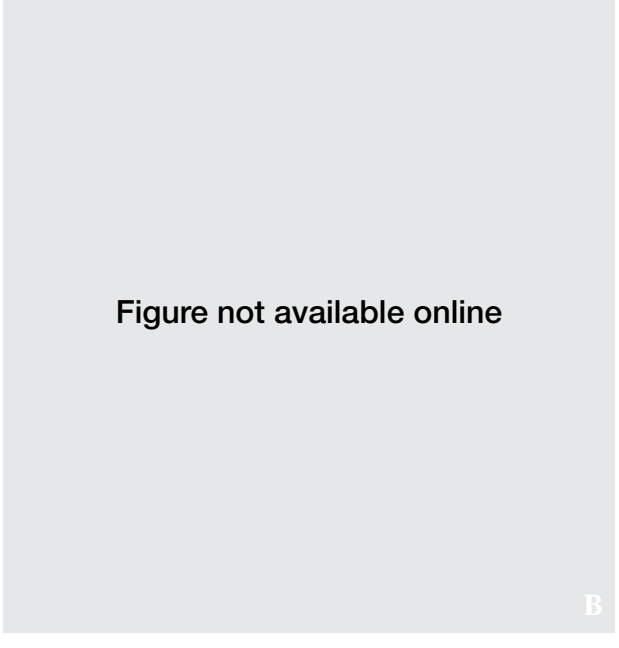


Figure 2. Frontal view before poly-L-lactic acid (PLLA) augmentation (A). Frontal view after PLLA augmentation showing improvement in nasolabial folds, zygoma, and bilateral temporal areas (B).

We recommend that injectors be comfortable with the notion that nonvisible papules may occur even with perfect technique and that these papules require no intervention and resolve within 18 months. Discussing this possibility in the informed consent and consultation is helpful. Patients who know what to expect do well.

High-dilution, high-volume filler injected with the proper technique provides a new approach to the use of PLLA and may confer a better side effect profile. The particles of PLLA are synthetic polymers of the α-hydroxy acid family that are 40 to 63 μm in size, with a molecular weight of 140,000 Da, and are suspended in sodium carboxymethylcellulose and mannitol.[14] It is believed that high dilution allows for a more uniform distribution of the product particles and less clumping. This is highlighted by the high level of patient satisfaction seen in our participants. Our investigation used both the tunneling crosshatch injection technique and the depot injection technique, depending on the location of injection. In addition to the nasolabial folds, we involved off-label injection sites at the mandible, cheeks, upper zygoma, and temporal regions (Figure 2), providing support that the high-dilution method is less likely to promote nodule formation in diverse areas of the face. Although there are a few studies that refute this, in general, there appears to be an inverse relationship between volume dilution and the incidence of nodules.[1,13]

In summary, our work suggests that a higher dilution of PLLA may serve to diminish the incidence of nodules and papules at injection sites.

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