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Injectable Poly-D, L-lactic Acid in Facial Rejuvenation: Three Case Reports

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Review Article

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Abstract

Injectable poly-D,L-lactic acid (PDLLA) is a biocompatible, biodegradable, and biostimulatory substance that is used as a new soft tissue filler. This article discusses the cases of three patients who received facial injectable PDLLA administration. It also provides an overview of PDLLA microsphere studies and adverse events of injectable PDLLA. Animal studies have identified hybrid tissue formation inside polymeric microspheres. Clinical studies on PDLLA injection with long-term follow-up in nasolabial fold correction and penis shaft augmentation have demonstrated its efficacy and safety. In 2014, injectable PDLLA was first approved by the Korean Food and Drug Administration for facial cosmetic applications. From April 2014 to July 2018, approximately 16,000 patients received facial PDLLA filler injections in Korea. No severe adverse effects apart from one infection and five nodule formations were reported. We also compared injectable PDLLA with its identical form, i.e, injectable poly-L-lactic acid (PLLA). PDLLA microspheres differ from those of PLLA in microparticle morphology, reconstitution time and water volume, needle clogging rate, nodule formation rate, collagen formation pattern, and longevity. Injectable PDLLA possesses all the features of ideal filler. However, further studies are required to better understand injectable PDLLA.

Keywords: AestheFill; PDLLA; PLLA; Microspheres; Biostimulatory; Filler

Introduction

Aging leads to both facial soft tissue depletion and bony change [1,2]. Treatment with injectable fillers is a simple, minimally invasive method of restoring the depleted soft tissue volume. Many types of fillers are available in the market. Polylactic acid (PLA) is an aliphatic polyester and is derived from renewable and degradable resources, such as corn and rice [3]. PLA and its degradation products H_2O and CO_2 are neither toxic nor carcinogenic to the human body, making them excellent materials for biomedical applications, including resorbable sutures, plates, screws, clips, and drug delivery systems [3-10]. Additionally, PLA is strongly hydrophobic and a biostimulator (ie it can elicit an inflammatory response from the tissues of living hosts) [3]. Lactic acid is a chiral molecule and has two enantiomers: L- and D-lactic acid. These two enantiomers can produce four distinct PLA substances: poly-D-lactic acid (PDLA), poly-L-lactic acid (PLLA), poly-D,L-lactic acid (PDLLA), and meso-PLA [3,11]. In biomedical research, only PLLA and PDLLA have been extensively studied and have been proven to be promising [4,12,13].

In 1999, to increase the volume of depressed skin areas, injectable PLLA (New-Fill; Biotech Industry SA, Luxembourg) was approved for use in Europe [14]. In August 2004, injectable PLLA (Sculptra; Dermik Laboratories, Bridgewater, the Netherlands) was approved in the US for the treatment

of HIV-associated facial lipoatrophy [15]. In 2009, the use of injectable PLLA was expanded to facial cosmetic applications [16].

In 2014, injectable PDLLA (AestheFill; Regen Biotech, Seoul, Korea), a newly developed biostimulator, was first approved for facial cosmetic use in Korea. Some countries or regions in the world have also approved its use in recent years. For better understanding of injectable PDLLA, we provide the cases of three patients who received administration of injectable PDLLA, an overview of injectable PDLLA studies, and adverse events of this newly developed soft tissue filler. Finally, we compare injectable PDLLA with its identical form, ie, injectable PLLA.

Case Reports

Case 1

A 30-year-old female presented with mild facial lipoatrophy. She asked for a biostimulatory volumizing product that is biodegradable and long-lasting for more than one year. She had no history of cosmetic augmentation and was considered a suitable candidate for injectable PDLLA based on the need for volumetric enhancement in the depletion regions. Upon evaluation, the patient was found with soft tissue depletion over her glabellar, supra-eyebrow frontal, temporal fossa, malar, sub-malar, cheek, nasal labial fold, anterior mandibular border regions, and mild black eye circles with tear troughs (Figure 1a,b).

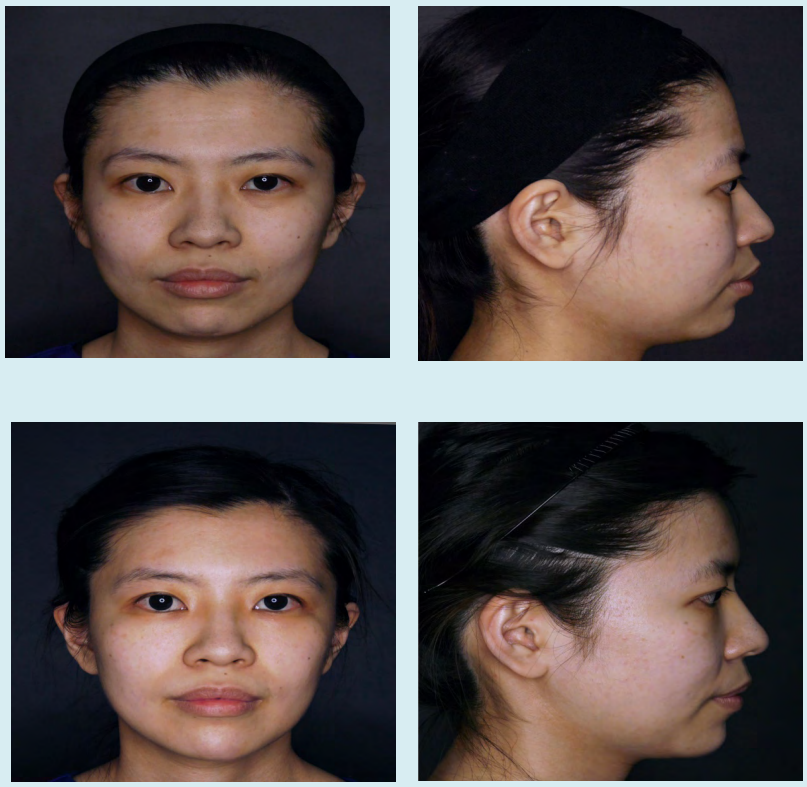

Figure 1: Case 1. A 30-year-old female received five sessions of PDLLA injections, 2–4 vials per session, spaced more than one month apart. The injection sites were glabella, forehead, temporal fossa, nasal dorsum, malar, sub-malar, cheeks, nasolabial folds, anterior mandibular borders, and chin. (a) Preoperative frontal view; (b) preoperative lateral view; (c) postoperative frontal view; and (d) postoperative lateral view (Photographs courtesy of Chuan-Yuan Lin, MD).

She also wanted to augment her nasal dorsum. She received five sessions of injections; total 16 vials of injectable PDLLA were used. Each session was separated at least one month apart. Injection of PDLLA filler in 2–4 facial regions were performed in one session. The injection layer of glabella, forehead, chin, and nasal dorsum regions was supra-periosteum, whereas the injection layer of the other facial regions was subcutaneous. A vial of injectable PDLLA was reconstituted by 3 ml sterile water for Injection (SWFI) and 1ml of 2% lidocaine solution. Using fanning method by 25G cannula, 7 vials of injectable PDLLA were injected in temporal fossa, glabella, and forehead regions in the 1st and the 3rd session; 6 vials of injectable PDLLA in malar, sub-malar, and cheek regions in the 2nd and the 5th session; and

2 vials of injectable PDLLA in anterior mandibular border region in the 4th session. Another vial of injectable PDLLA was reconstituted by 1ml SWFI and 0.5ml of 2% lidocaine solution, with bolus injection by 25G needle in nasal dorsum (0.5ml) and chin (1ml) in the 4th session. Postoperative views of three months after the 5th session of injection showed good effect over all the injected regions, with a more harmony look (Figure 1c,d). Note that the forehead wrinkles diminished, lateral eyebrows slightly elevated, and the black eye circles disappeared. This result was persistent on follow-up at 12 months. No adverse effects like nodule formation were found. The patient was satisfied with the result.

Case 2

A 54-year-old male presented with moderate facial lipoatrophy. He had no history of cosmetic augmentation and was considered a suitable candidate for injectable PDLLA. Upon evaluation, the patient was found with obvious soft tissue depletion over his bilateral temporal fossa, malar, sub-malar, and cheek regions (Figure 2a,b). He received two sessions of PDLLA injection over these regions, with four vials per session spaced 2 months apart. The injection layer was subcutaneous. A vial of injectable PDLLA was reconstituted by 3 ml SWFI and 1ml of 2% lidocaine solution. In each session, using fanning method by 25G cannula, 3 vials of injectable PDLLA were injected in temporal fossa; 1 vial of injectable PDLLA in malar, sub-malar, and cheek regions. Postoperative views of four months after the 2nd session of injection showed good effect over these injected regions (Figure 2c,d). This result was persistent on follow-up at 15 months. No adverse effects were found.

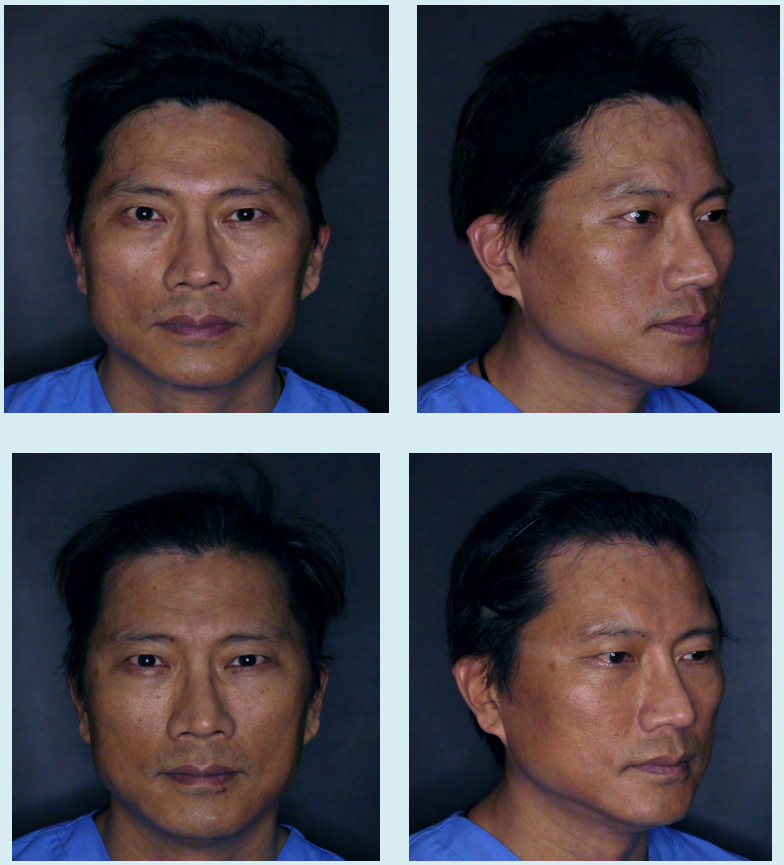

Figure 2: Case 2. A 54-year-old male received two sessions of PDLLA injections, four vials per session, spaced two months apart. The injection sites were temporal fossa, malar, sub-malar, and cheeks. (a) Preoperative frontal view; (b) preoperative oblique view; (c) postoperative frontal view; and (d) postoperative oblique view (Photographs courtesy of Chuan-Yuan Lin, MD).

Case 3

A 62-year-old female presented with moderate facial lipoatrophy. She had ever received HA injection over her middle face and neuromodulator therapy for her forehead and glabellar regions. Upon evaluation, the patient was found with soft tissue depletion over her bilateral temporal fossa, and cheek skin sagging with pre-jowl sulcus. (Figure

3a,b) She received 2 vials of PDLLA injection over bilateral temporal fossa and lower face. The injection layer was subcutaneous. A vial of injectable PDLLA was reconstituted by 6ml SWFI and 2ml of 2% lidocaine solution. Postoperative views of 6 months after injection showed good effect. (Figure 3c,d) This result was persistent on follow-up at 12 months. No adverse effects were found.

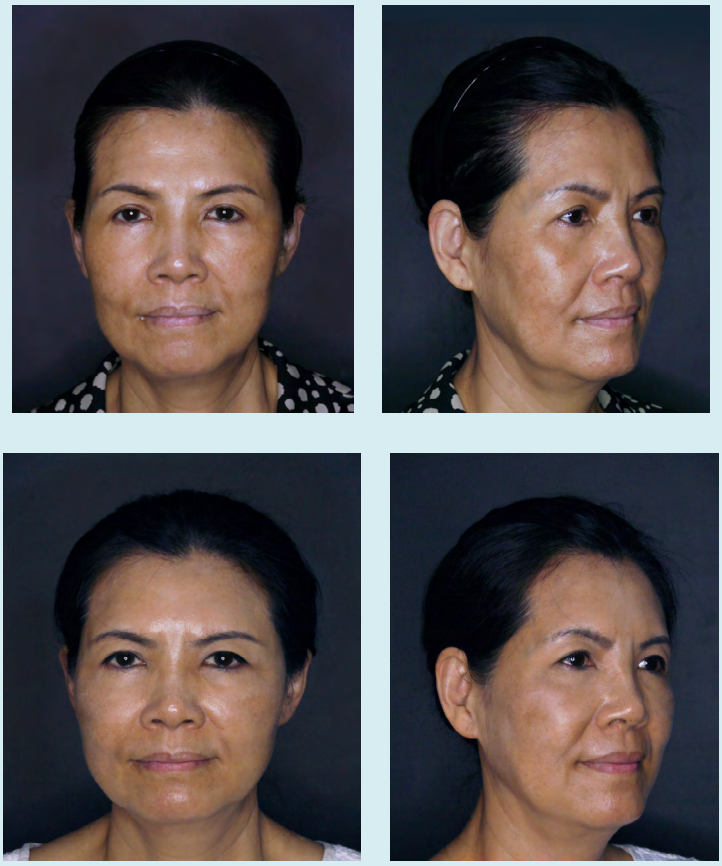

Figure 3: Case 3. A 62-year-old female received one session, two vials of PDLLA injection. The injection sites were temporal fossa and cheeks. (a) Preoperative frontal view; (b) preoperative oblique view; (c) postoperative frontal view; and (d) postoperative oblique view (Photographs courtesy of Jui-Yu Lin, MD).

Discussion

Preclinical animal study [17] on the efficacy and safety of PDLLA microspheres was performed between September 2009 and May 2011. PDLLA microspheres were injected as a bulking substance into the subcutaneous tissue of rats. The injected volume was maintained from the 2nd week to the 20th week post injection. There were no abnormal findings around the injected site. PDLLA microspheres were localized in the subcutaneous tissue without migration to surrounding tissues and other distal organs. Inflammatory cells were observed around the PDLLA microspheres at the 2nd week post injection; however, they tended to decrease at the 4th week. Cells, actin, and type-1 collagen were found in the injected PDLLA mass, not only between but also inside the PDLLA microspheres, with a progressive increase from the 2nd week to the 20th week post injection. This animal study confirmed the efficacy and safety of PDLLA microspheres as subdermal fillers.

From August 2012 to March 2013, a randomized, evaluator-blinded, comparative study [18,19] on the efficacy and safety of injectable PDLLA compared with HA for the correction of nasolabial folds was conducted at Chung-Ang University Hospital and Seoul Asan Medical Center, Korea. In total, 58 subjects (30 in the PDLLA group and 28 in the HA group) completed the follow-up at 24 weeks. The results showed that both PDLLA and HA injections were well tolerated and that adverse effects were mild and transient in most cases. Further, injectable PDLLA provided noninferior efficacy compared with HA after being used for treating moderate-to-severe nasolabial folds. Of the 58 subjects, 30

completed a 24-month long-term safety evaluation [20]. During the 24-month follow-up, 13 cases of adverse effects (arthralgia, gingival pain, musculoskeletal pain, urticaria, and gastrointestinal symptoms) were identified. However, these were unrelated to PDLLA injection and were not severe. The maximum improvement in the nasolabial fold Wrinkle Severity Rating Scale (WSRS) scores was observed at the 6th month's follow-up. Despite the WSRS scores were gradually normalized, they were still better at the 24th month's follow-up than at the preoperative status.

Between June and November 2012, another prospective, single-arm, multicenter study [21] was performed to evaluate the efficacy and safety of injectable PDLLA in penile augmentation with a follow-up period of 18 months. The results showed that penile PDLLA injection has a significant augmentative effect on the penis for up to 18 months and that it is well tolerated without serious adverse effects.

According to the manufacturer's investigation, which was performed by questionnaire in August 2018, from April 2014 to July 2018, with the Korean FDA's approval, approximately 16,000 patients received facial injectable PDLLA filler injections in Korea. No serious adverse effects (ie death, blindness, and skin necrosis) were reported during this period. Most of the adverse effects reported were early-onset: mild swelling (50% of all patients), bruising (30%), and pain (20%). All patients recovered with ice packing and medication. The other adverse effects reported were late-onset. One patient with bacterial infection 10 days post injection recovered after oral antibiotic administration (Cephalosporins) for 2 weeks. Five patients with nodules (three at infraorbital region and two at nasolabial region) were reported. The nodules were treated by injection of SWFI into the nodule followed by a strong massage. After treatment for one to two sessions, all the five patients subsequently recovered. Seok, et al. [22] reported one patient with granuloma over nasolabial region after PDLLA microspheres injection that was successfully treated by ultrasonography guided curettage. Although these findings were gleaned from questionnaire rather than a randomized, controlled trial, these data showed that the incidence of infection, nodules, or granuloma formation after injectable PDLLA administration was low.

The main ingredient of injectable PDLLA and injectable PLLA are both composed of PLA microparticles, are biocompatible and biodegradable polymers, and are biostimulators [17]. A vial of injectable PLLA contains 150 mg of PLLA microparticles, 90 mg of CMC, and 127.5 mg of nonpyrogenic mannitol; whereas a vial of injectable PDLLA contains 154 mg of PDLLA microparticles and 46 mg of CMC [19]. The microparticles of injectable PDLLA range from 30 to 70 μm, [17,19] whereas those of injectable PLLA range from 40 to 63 μm [15,23]. The microparticle size of the two products is large enough to not be phagocytosed by various cells found in the skin [24-26] and small enough to pass through an injection needle or cannula. The PDLLA microparticles are spongiform microspheres [17], whereas those of PLLA are irregular in shape with a solid structure [15].

Both injectable PDLLA and injectable PLLA are supplied as a lyophilized powder [19]. For one vial of injectable PDLLA, 1.4–8 cc SWFI is used for reconstitution as recommended by the manufacturer, and the reconstitution time is about 20–30 minutes. Conversely, for one vial of injectable PLLA, 7–8 cc SWFI is needed for reconstitution and the suitable reconstitution time is more than 24 hours [27]. For injectable PDLLA, the injection is administered via the linear threading and/or depot technique. The treatment plane is subcutaneous and/or supra-periosteum. During injection, the injection sites are regularly massaged to evenly spread the product. However, unlike injectable PLLA [23], postoperative massage is not required. Excessive correction or injection in a single treatment is prohibited, and another injection, if required, should be given after a gap of at least 1 month.

Clinically, when performing PLLA injection, needle clogging and/or post-injection subcutaneous nodule formation occurs sometimes, particularly with an insufficient volume and reconstitution time [28,29]. When PDLLA is injected instead of PLLA, needle clog and post-injection subcutaneous nodule formation seldom occurs. The amount of SWFI needed for the reconstitution of a vial of injectable PDLLA can be reduced to 1.4 cc. A homogeneous suspension of injectable PDLLA with few micro-clumps indicates that needle clog and nodules formation are less likely to occur. Clinical studies [18,20] on this 1.4 cc SWFI reconstitution method had shown only mild and transient adverse effects in most cases. No nodule formation was reported.

Like biostimulators, injectable PLLA microparticles elicit subclinical foreign-body inflammatory responses in the host, resulting in encapsulation of the microparticles followed by fibroplasia and type-1 collagen deposition in the extracellular matrix [30,31]. Both animal model and human clinical studies have demonstrated collagen formation induced by PLLA microparticle injection [32-35]. Also, the collagen stimulatory effect of injectable PDLLA have been confirmed [17,36]. The collagen deposition sites induced by PDLLA microspheres are different from those induced by PLLA microparticles. Because of spaces between and inside PDLLA microparticles, the major collagen deposition sites are inherent empty spaces. Animal studies [17,36] have reported that in addition to new tissue proliferation, collagen and actin deposition becomes evident in microspheres

between 8 and 16 weeks.

The observed volume effect of injectable PLLA has a dual mechanism of action. Initially, it is caused by the hydrogel volume injected. However, the immediate fill effect diminishes within 1 week as the water is absorbed and swelling subsides, leaving only PLLA microparticles in place. The secondary delayed mechanism of action involves collagen synthesis. A capsule of macrophages, lymphocytes, mast cells, and fibroblasts surrounds these particles 1-month post injection. Subsequently, the thickness and cell density of this capsule decrease gradually, and at 6 months, the surrounding areas are composed entirely of collagen fibers [15,37]. Consequently, the volume effect in the secondary phase can be observed gradually. In the case of PDLLA, the initial volume effect of injectable PDLLA is also due to the total hydrogel volume injected. However, according to animal studies, [36,38] the volume reduces to 65%–70% of the initial injected volume and is then maintained for 24 weeks [36]. This reduced volume might be a result of the absorption of water and CMC [36,38]. This phenomenon is consistent with our clinical observation in human injections. PDLLA microspheres possess multiple micropores, providing a scaffold for actin and collagen formation inside the microspheres [17,36]. Growing inside, the newly formed collagen does not increase the total volume; therefore, the observed volume does not change. In contrast, the PLLA-induced collagen formation is from the capsule surrounding the microparticles. The observed volume increases gradually when collagen develops.

On an average, the volume correction period using injectable PLLA is up to 24 months or possibly longer [14,32,39,40]. The same with injectable PLLA, according to the 24-month follow-up study [20] of a clinical trial of injectable PDLLA, the improvement in the nasolabial fold WSRS scores was still good at the 24-month follow-up.

Conclusions

Injectable PDLLA is new soft tissue stimulatory filler. This article provides three patients who received facial PDLLA microspheres injection, overview of PDLLA microspheres studies, and comparison of PDLLA with PLLA. Although PDLLA has the same chemical formula as PLLA, they differ in the shapes of their microparticles. The microparticles of PDLLA are sponge-like microspheres, whereas those of PLLA are irregular in shape with a solid structure. Injectable PDLLA is biocompatible, biodegradable, biostimulatory, and long-lasting. It also has a short reconstitution time, needs little water for reconstitution, and has a lower complication rate compared with PLLA. Additionally, injectable PDLLA possesses all features of ideal filler. However, further studies are required to better understand injectable PDLLA.

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