Preliminary Report

Changes in Dermal Thickness in Biopsy Study of Histologic Findings After a Single Injection of Polycaprolactone-Based Filler into the Dermis

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Abstract

Background: During aging, facial skin thins, atrophies, and loses elasticity. Subdermal filler injections can volumize and treat wrinkles but cannot directly change dermal thickness. Polycaprolactone (PCL) fillers can improve skin texture and quality through dermal thickening and inducing neocollagenesis. Through biopsy study, evidence of neocollagenesis will be introduced.

Objectives: In this single-clinic prospective study, 13 patients received a single injection of diluted 0.5 cc of PCL filler in the facial dermis except the right temple area for intra-individual control study.

Methods: A biopsy was performed from temple skin at 1 year for all patients. An additional biopsy was performed at 2 weeks and 4 years posttreatment for 3 patients. Dermal thickness was measured with sonography after 1 year.

Results: On average, the mean rate of temporal skin thickness in biopsy specimens (n = 117 points in 13 patients) at 1 year posttreatment increased by 26.74% ± 9.26% from 1412.41 μm ± 69 μm to 1781.11 μm ± 110 μm (P < 0.001). On average, the mean thickness of facial skin (n = 39 points in 13 patients) measured by ultrasound at 1 year increased by 21.31% ± 4.34%. Around PCL particles, many fibroblasts, giant cells, new capillaries, new collagen, and elastic fibers were found in various stains.

Conclusions: Facial dermal thickness increased after intradermal injection of PCL filler by neocollagenesis to treat skin atrophy. PCL filler may last more than 4 years in the dermis.

Level of Evidence: 4

During aging, the facial skin undergoes atrophy, becomes thinner, loses elasticity, and develops larger pores. Therefore, along with volumizing treatments for the aging face, facial treatment for improving skin texture is highly sought after. Subdermal filler injections can volumize and treat wrinkles but cannot directly change the dermis; for example, the injection lifts up the dermis but rarely thickens it.
such as poly-L-lactic acid-based, calcium hydroxyapatite (CaHA)-based, and polycaprolactone (PCL)-based fillers, can not only improve skin texture but also improve skin texture and rejuvenate skin by inducing neocollagenesis and volumization.4–11 PCL-based filler is an injectable implant consisting of 30% PCL microspheres (approximately 40 µm in diameter) suspended in a 70% sodium carboxymethylcellulose (CMC) gel carrier.4,12

This study focuses on dermal thickening (different from the volumizing filler injection) and long-term tissue reactions in the dermis. A total of 13 patients participated in the study. Patients received a single injection of 3 cc of diluted PCL (0.5 cc) filler on the facial dermis, including on the forehead, anterior cheek, and temple but not on the right temple for an intra-individual control study. At 1 year posttreatment, patients received planned temple-lifting surgery. During the surgery, biopsy specimens were obtained to evaluate dermal thickness and histologic reaction under light microscopy. Neocollagenesis and fibroblast aggregation around the PCL spheres were also observed with biopsy study. The evidence of this was introduced by various special staining methods. Skin thickness was then measured by ultrasonography. At 2 weeks and 4 years posttreatment, additional biopsy specimens were obtained from only 3 patients to evaluate initial and late tissue reactions.

Clinical trials (intradermal injection of PCL filler) resulted in a marked and prolonged increase in skin thickness and skin quality satisfaction by the patients. The objectives of this study were to evaluate (1) dermal thickening, (2) tissue reaction in the dermis, (3) longevity of PCL particles in the dermis, and (4) incidence of adverse effects following intradermal PCL-based filler injection.

In this study, histologic analysis of biopsy samples obtained at 1 year posttreatment showed that the injected PCL particles, mainly in the intradermal layer, were smooth (without damage) and round spheres of 40 µm diameter, on average. Furthermore, histologic analysis of biopsy at 4 years posttreatment showed that the particles became small, cleaved, rough, and irregular spheres. However, the particles were present, leading to the conclusion that the PCL-2 longevity in the dermis may be longer than 4 years.

**METHODS**

Informed consent from the patients was obtained in compliance with the Korean Society of Plastic and Reconstructive Surgeons standards. This study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as well as to applicable local regulations. This was a single-clinic prospective study from December 2012 to December 2017 including 1-year and 4-year follow-up periods.

All eligible 13 patients underwent clinical evaluation, including medical history recording and limited physical examinations. They had all been patients of the author’s clinic. Previously they were injected with botulinum toxin, but not within 6 months before the study. Patients who had received filler injections or laser and chemical peels prior to this study were excluded, no matter how long ago they had these procedures, because these procedures would influence the production of collagen. All 13 patients agreed to have no cosmetic procedures during the follow-up period, including injectables such as fillers or Botox and energy-based devices such as high-intensity focused ultrasound, because these would interfere with the results.

Biopsy studies were performed to measure the dermal thicknesses of biopsy specimens using a light microscope (Olympus BX41, Olympus Corporation, Tokyo, Japan) and a microscope digital camera (eXcope T300, Touptek, Zhejiang, P.R. China) at 1 year posttreatment with the M-version PCL-based filler (Ellanse-M [PCL-2], Sinclair Pharmaceuticals, London, UK). Additional biopsy studies were performed for only 3 patients to evaluate initial and late tissue reactions at 2 weeks and 4 years posttreatment.

Changes in skin thickness after the procedure were measured by ultrasonography on 3 points on the face. In addition, all patients received facial digital photography at every follow-up visit to assess skin texture.

**Patient Selection**

A total 13 patients who had thin skin participated in the study. Patients were included if they demonstrated thin skin with skin atrophy due to aging and had moderate-to-severe levels (Class II and III in Fitzpatrick’s Classification13) of wrinkles on their faces.

**Injection Methods**

All patients were treated with 1000 injections in the dermis with a small quantity (0.0005 cc) of PCL filler after the topical application of a 9% lidocaine cream. To reconstitute the injection solution, 0.5 cc of PCL filler, 0.5 cc of lidocaine, and 2 cc of normal saline were mixed. This mixture was made by adding the 3 ingredients into a 3-cc syringe then removing all air bubbles. Once no air bubbles were present, the first 3-cc syringe was attached to a connector and the second syringe. After removing air bubbles one more time, the mixture was passed though the 2 syringes 20 times to ensure it was homogeneously mixed (Video, available online as Supplementary Material at www.aestheticsurgeryjournal.com).

Using an automatic injector (Vital Injector, Ensung Global, Korea) with 31-G multi(5)-needles,4 all patients...
received an intradermal injection of 3 cc of diluted PCL-2 filler on the facial dermis, including on the forehead, anterior cheek, and temple except near the eyelid, but not on the right temple for an intra-individual control study (Supplemental Figures 1 and 2, available online at www.aestheticsurgeryjournal.com).

Dilution lowers the viscosity of the CMC gel carrier portion to facilitate injections with five 31-G needles on the injector. To reduce the injection time and operator effort during intradermal injections, an automatic injector was used to deliver a small volume (0.001 cc of diluted PCL filler, 0.0005 cc of PCL filler at one injection site) of diluted PCL filler at each injection site with consistent injection depths. To deliver 3 cc of diluted PCL filler, 200 sets of passes (strokes) were performed to cover 1000 injection sites; because the injector has 5 needles, one stroke of the needle heads constitutes 5 injection sites. The needle part features a suction cup that can hold skin tightly to prevent displacement of the dermis. To keep more distance between the blood vessels and, in this study, the target of injection was the deep dermis (Supplemental Figure 1, Video).

The distribution of micro-droplet injections was systematic at 5 mm. The usual treatment area on the face is approximately 32,800 mm². The treatment area of a 5-pin needle head is 166 mm² (12.9 mm × 12.9 mm). Therefore, 200 passes (196 = 32,800/166) of shots can cover the whole face, and 200 passes (strokes) with a 5-pin needle produce 1000 injection sites. The injection depth was deep dermis, which is the 1-mm setting on the injector (the injection depth of the injector can be controlled from 0 to 2 mm.). The injection amount per pass was 15 µL, making the injection amount per injection site 3 µL (because 0.5 cc of PCL filler was 1:5 diluted, the actual amount of PCL filler per injection site was 0.5 µL) (Supplemental Figure 1). After evenly distributing the PCL fillers over the entire face, the remaining PCL fillers were injected with 20 to 40 strokes on the nasolabial fold (Supplemental Figure 2). The author’s technique (intradermal injection utilizing an injector) was first developed in 2009, and the author has obtained a patent from the Korean Intellectual Property Office.

After the procedure, to relieve pain and ecchymosis and to help the PCL filler material spread, a cold wet gauze (10 cc of normal saline with 0.1 cc of vitamin K) was applied to the face, and cold compression was performed for 10 minutes. None of the patients had touch-up because PCL longevity is quite long.

**Biopsy Study**

A biopsy study was performed from the skin of both temples of patients who had planned to undergo a temple-lifting surgery at 1 year. An additional biopsy study was performed at 2 weeks and 4 years posttreatment for 3 patients (39-, 41-, and 43-year-old females).

A 1- × 5-cm piece of soft tissue was excised from an area parallel to and just below the temporal hairline during the temple-lifting surgery. The thickness of temporal skin was measured at 9 points in 3 different biopsy slides for each patient. Using the SAS 9.4 program, a paired t test was performed to measure the statistical significance level.

To evaluate tissue reaction, such as the synthesis of collagen and elastin fibers, various special stains were used: Masson’s trichrome, Picrosirius red, collagen I and III antibody (immunohistochemistry), Victoria Blue (VB), Verhoeff’s Van Gieson (EVG), and H&E stains.

**Ultrasound Skin Thickness**

Skin thickness on 3 points (1. temporal skin point: midpoint between the hair line and eyebrow on the vertical line of the lateral canthus; 2. anterior cheek point: midpoint between the lateral canthus and mouth corner; and 3. midpoint on nasolabial fold between the alar and the mouth corner) was measured utilizing ultrasonography after a single intradermal injection of PCL-2 filler. Although care was taken to not press down hard, some may argue that the dermis becomes thin when it is pressed down by ultrasound. However, when dermis is not pressed down hard enough, the fat compartment thins, not the dermis.

**RESULTS**

**Skin Thickness in Biopsy Study**

The mean age of the patients was 38.7 years (range, 28-68 years), and all were Asian females. On average, the mean rate of temporal skin thickness in biopsy specimens
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Table 1. Changes in Skin Thickness on Biopsy Specimens (×40)

| Biopsy time | Control | 2 weeks | 1 year | 4 years |
|-------------|---------|---------|--------|--------|
| Dermal thickness (n = 23) | 1412.41 ± 69 | 1781.11 ± 110 |
| Increased % to control | 26.7% |
| Dermal thickness (n = 3) | 1389.52 ± 45 | 1862.55 ± 84 | 2066.7 ± 31 |
| Increased % to control | 2.03% | 34.0% | 48.7% |

The mean thickness of the 23 control temporal skin samples was 1412.41 μm ± 69.2 μm and the thickness of the treated temporal skin was 1781.11 μm ± 110.6 μm at 1 year. The increase in dermal thickness of 26.7% after 1 year was statistically significant (P < 0.001). In 3 females, the mean thickness was 1389.52 μm ± 45.1 μm at 2 weeks, 1862.55 μm ± 84.8 μm at 1 year, and 2066.70 μm ± 31.1 μm at 4 years.

![Figure 1](https://academic.oup.com/asj/article-abstract/39/12/NP484/5336281/501x501)

**Figure 1.** Changes of dermis thickness on the temporal area. In this study, the skin thickness was measured from the epidermis to the skin appendage. (A) One year after posttreatment, the dermal thickness of temple skin on the control (right) side was 1412.41 μm ± 69 μm. (B) One year after posttreatment, the dermal thickness of temple skin on the treated (left) side was 1781.11 μm ± 110 μm, a 26.7% increase from the control side. Black arrows, polycaprolactone particles.

Fibroblasts

At 2 weeks, 1 year, and 4 years posttreatment, many fibroblasts were found near PCL particles (Figure 2F).

Foreign-Body Giant Cells

Numerous PCL particles were found via microscopy at 2 weeks posttreatment. Approximately half of these particles were surrounded by a foreign-body giant cell (FGC) per PCL particle. Fusing of macrophages to FGCs started at 2 weeks in response to the presence of a foreign body larger (40 microns) than macrophages. The rest were surrounded by macrophages (Figure 2A,B). The mean of the long axis of macrophages was 10.53 ± 1.41 microns, and that of the short axis was 5.36 ± 1.08 microns (Figure 2A).

However, at 1 year and 4 years posttreatment, all PCL particles were surrounded by an FGC (Figure 2C,E). An asteroid body was found in the FGCs at 4 years (Figure 2E). There is debate on the composition of asteroid bodies. Some research studies indicate they are composed of lipids arranged into bilayer membranes, and others indicate they are related to centrioles. However, nothing is absolutely clear.

The difference between Langhans’ giant cells and FGCs is the location of nuclei: Langhans’ giant cell nuclei are located near the outer side of the cell, and in FGCs they...
are in the middle of the cell. Research results seem to indicate Langhans' giant cells, not FGCs, because nuclei are pushed aside due to the PCL particle.

**Monocytes**
The number of monocytes was determined at 2 weeks (Figure 2A,B). Numerous monocytes were found at 1 year (Figure 2C).

**New Capillaries**
New capillaries featured a small lumen, were composed of thin endothelium, and contained 1 or 2 red blood cells. It was difficult to spot new capillaries at 2 weeks. However, at 1 year, the number of new capillaries increased, and at 4 years, this number increased even more. Three new capillaries were found in 10 slides (×400) at 1 year, and 19 new capillaries were found in 10 slides (×400) at 4 years (Figure 2E,F).

**Eosinophils**
Eosinophils were not found in any of the slides at 2 weeks. Five eosinophils were found in 10 specimen slides at 1 year.
under 400 × magnification (Figure 2D). Three eosinophils were found in 10 slides (×400) at 4 years (Figure 2E,F).

**Plasma Cells**
There were no plasma cells in any of the slides. This finding is different from other case studies performed by the author, in which plasma cells were found in granulomas after PCL injection.

**New Collagen Fibers**
The existence of new collagen fibers was evaluated by H&E staining, Herovici’s staining, Masson’s trichrome staining, and immunohistochemistry (collagen I and III antibody). It was difficult to find them at 2 weeks, whereas numerous were found at 1 year and 4 years.

In Herovici’s staining, young (newly made) collagen fibers were stained blue, and mature collagen fibers were stained red. In immunohistochemistry of collagen I and III antibody, denser staining zones were found close to the circumference of each PCL particle. In Masson’s trichrome staining, preexisting collagen fibers were regular in pattern, with a similar depth of blue color. At 1 year, there were a number of new collagen fibers; they were extremely thin and located between particles. At 4 years, there were more of them (Figure 3).

**New Elastic Fibers**
More irregular and short patterned elastic fibers were found in the VB staining and EVG special staining at 1 year and 4 years posttreatment (Figure 4) than at
2 weeks. Whereas new collagen fibers were located between particles, new elastic fibers were located throughout.

**CMC Carrier Gel**

In the H&E staining, FGCs and macrophages were also observed around CMC, engulfing the CMC portion (Figure 2B). CMC carrier gel in PCL filler was located at 2 weeks but not at 1 year and 4 years.

**Diameter of PCL Particles**

PCL filler at 2 weeks and 1 year was smooth on the surface, sphere-shaped, and approximately 40 μm. The average of diameter of the PCL particles at 2 weeks was the same as at 1 year (Figure 2A-C). However, at 4 years, the PCL filler particles decreased and were irregular with rough surfaces, and almost all were cleaved (Figure 2E).

**Longevity of PCL-2 Particles**

The observation of PCL-2 particles at 4 years proved their persistence or longevity in the dermal layer for at least 4 years (Figure 2E).

**Skin Thickness in Ultrasound Imaging Study**

One year after receiving injection, all patients underwent an ultrasound assessment of skin thickness at 3 points (temporal, anterior cheek, and nasolabial fold). The
mean rate (n = 39) of dermal thickness increase was 21.31% ± 7.68% of the baseline. Ultrasonography confirmed that the skin thickness gradually and slightly increased in all patients after the dermal injection of PCL filler, with visible improvement of skin texture and fine wrinkles (Figure 5).

**Adverse Events**

There were no serious adverse events, such as infection, granuloma, embolism, skin necrosis, skin irregularities, nodules, dermal lumps, or prolonged pain, at any follow-up timepoints, and none of the patients discontinued the study due to adverse events (Figure 6). There were no visible dermal lumps, because the injected amount of the PCL filler was 0.0005 cc per site. Through the light microscope at 40× magnification, no elevation of the dermis was observed (Figure 1).

All patients experienced mild swelling for 1 or 2 days, but none of the cases of infection or prolonged swelling lasted more than 5 days. Seven patients (53.8%) experienced ecchymosis on injection sites, especially on thinner skin areas, for 2 or 5 days due to injection using multiple sharp needles on 1000 sites.

**Figure 6.** Changes in skin texture and skin pores for this 41-year-old female who was also featured in Figure 5. (A) Before the treatment and (B) 1 year after polycaprolactone injection, pore size (in the anterior malar area) was reduced. The nasolabial fold also showed significance. The appearance in both the increase of skin thickness and anteromedial cheek volume enhancement changed. Neocollagenesis in dermis and subdermis may lead to skin tightening. The skin tightening seems to have elevated the depressed area and flattened the nasolabial fold. There was a redistribution effect.
DISCUSSION

Mild swelling with slight redness for 1 or 2 days was observed in all patients due to multiple injection (1000) sites and irritation caused by the CMC carrier gel (which contains glycerin) in the PCL filler. Therefore, injection of a tumescent solution prior to the PCL injection is recommended to prevent swelling and pain after the procedure.\(^\text{19}\)

Ecchymosis was found on thinner-skinned patients on thinner skin areas. For thinner-skinned patients, it is unavoidable to place a needle on the subdermal plexus, thus leading to the creation of ecchymosis. In biopsy specimen evaluation, the injection was performed in the deep part of the dermis. However, about 20% of the filler materials were found under the dermis. In this clinical trial study, PCL filler was injected into the dermis. However, the manufacturer’s manual recommends not to inject the PCL filler near the dermis and, furthermore, not into the dermal layer because superficial injection has a high risk for producing dermal lumps, which cannot be treated long-term. When utilizing the PCL filler, superficial injection (near the dermis or intradermis) is not recommended for usual patients and by usual doctors. Therefore, inexperienced doctors struggle with my method and need to learn and be trained before this procedure. It is important that inexperienced doctors do not inject the dermis. If PCL filler is injected into the dermis without utilizing an injector or undiluted PCL solution, lumps are created that last a long time. Injection amount is also very important to prevent dermal lumps.

This report describes the results of a single-treatment study in which the skin thickens with improvement in skin texture, such as skin pore reduction. The measurement of dermal thickness utilizing ultrasonography is relatively precise. Many factors (such as measurement location and direction and contact pressure of the probe) can produce bias during the measurement of dermal thickness. Technically, the dermal thickness is slightly compressed or reduced by the pressure of a US probe, but it is not expended or thickened by pulling during evaluation with ultrasonography.

Aging skin can be treated and thickened by PCL intradermal injection, and neocollagenesis in the dermis can increase skin thickness. The improvements of skin texture, including skin pore and fine wrinkles, may correlate with neocollagenesis and dermal thickening effects after intradermal PCL injection (Figure 6). However, intradermal injection using PCL filler is not an easy method and is not recommended for usual doctors.

Because the surface (dermal-subdermal junction) between the fat and dermis is uneven, the skin thickness from the epidermis to the skin appendage was chosen to be measured. However, as shown in Figure 1, the dermis became thicker not only between the epidermis and the appendage but also noticeably between the appendage and the fat. Therefore, the actual difference in skin thickness may be even greater than that mentioned above. Many think that the skin thickens when filler is injected onto fat. However, collagen generation on dermis is not thoroughly made through this type of injection onto fat. To have an actual effect on skin, physicians must inject onto the dermis.

Numerous doctors confuse dermal injections with subdermal injections.\(^\text{14}\) Intradermal injections mainly work by producing dermal collagen and skin changes, such as an improvement in pores and fine wrinkles. Subdermal injections produce a volumizing effect and can treat skin folds, but they are ineffective for treating fine wrinkles or skin texture. To improve skin texture, injections should be performed near the dermis. However, this is not easy, and it usually has a high risk when doctors inject PCL filler into the dermis because the intradermal injection of PCL filler has significant risks for creating dermal lumps lasting for over 4 years. In the author’s clinical experience, PCL particles frequently persist at 2 years in the subdermis or fatty tissue and for more than 2 years in the dermis. Compared with loose fatty tissue, denser soft tissue in the dermis might interfere more with the movements and aggregation of histocytes. Lumps and bumps that are inadvertently caused by treatment may therefore persist for at least 4 years. Thus, the author’s technique using an injector or superficial injection is not recommended for less-experienced physicians.

The mechanism of neocollagenesis with a PCL-based filler is quite similar to that of the CaHA filler (Radiesse). Both particle sizes are approximately 40 microns, and they both have a smooth surface and fully round shapes. Both particles (30%) are suspended in the CMC portion (70%).\(^\text{20}\) CMC is absorbed during the first month, and the calcium particles remain. Differences in the two are the severity of tissue reaction and longevity of particles. In this study, eosinophils were found after PCL injection, whereas they did not appear after CaHA filler injection. The author recommends using CaHA filler injection before using PCL filler because CaHA filler has a shorter longevity. By this the author means that inexperienced doctors should initially use CAHA until they have gained enough experience.
and confidence in their ability to use a PCL due to the fact that if lumps are created, the duration is shorter when using CAHA (the author suggests short-term fillers to start with; once the doctor has gained more experience, longer lasting filler should be used.) The side effects (lumps or nodules) due to CaHA filler would spontaneously disappear after a year, but the side effects due to PCL filler would spontaneously disappear after 2 years, or sometimes longer than this.

The study mean patient age is slightly younger; the young patients are more worried about pores, whereas older patients are more concerned about skin tightening. For older patients, utilizing another skin-tightening method such as energy-based devices (Thermage Ulthera) should be considered before PCL injection. However, this study did not use energy-based devices, and patients were not permitted to use these devices for 1 year after the treatment. The results are from only the injections.

Many articles describe that the expected longevity of PCL-2 in vivo is 2 years. This longer term serial biopsy study first confirmed that PCL-2 had a longevity in the dermis of at least 4 years (even intradermal injection might have a longer duration than subdermal injection) (Figure 4C,G).

This study showed that there were numerous FGCs, macrophages, and monocytes, and some eosinophils, around the PCL particles (Figure 4E,F). Any small contamination during PCL injection may produce chronic granuloma with histocytes. Therefore, physicians should be extremely careful about contamination during the injection because even the slightest contamination can result in a biofilm, infection, nodule, and/or granuloma, which may last at least 4 years, and these side effects are intractable without the surgical removal of the PCL product. These side effects (transferred to the author’s clinic) were caused by contamination, mainly during the injection. Mild infection and biofilm were sometimes intractable with antibiotics, such as quinolone (Clavit Tab., 500 mg twice/d), for 2 or 3 weeks. Triamcinolone or 5-fluorouracil injections might last at least 4 years, and these side effects are intractable because even the slightest contamination can result in chronic granuloma with histocytes.

CONCLUSIONS

The dermis thickened after intradermal injection of PCL filler. Dermal thickening might be caused by neocollagenesis. Improvement of skin texture might be caused by neocollagenesis. Injectable PCL filler can be an effective treatment for skin atrophy, wrinkles, and pores. Longevity of PCL-2 (PCL portion) in the dermis may be more than 4 years. Around PCL particles, there are many fibroblasts and an uncountable number of FGCs and monocytes on H&E staining at 2 weeks, 1 year, and 4 years. Newly made capillaries were found at 1 year, and more were found at 4 years. New collagen fibers were found at 1 year and 4 years by Masson’s trichrome, Herovici’s, and collagen I and III antibody stainings. A high density of elastic fibers (irregular and short patterned) existed around PCL particles as shown by VB and EVG special stains. Through the biopsy study, neocollagenesis, neoe lastinogenesis, and neovascularization were all confirmed after PCL injection into dermis.

Supplementary Material

This article contains supplementary material located online at www.aestheticsurgeryjournal.com.

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