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Bio-characteristics and Efficacy Analysis of Biodegradable Poly Dioxanone Dermal Filler in a Mouse Model and Humans

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Abstract. *Background/Aim: This research investigated the biophysical properties, safety, and efficacy of polydioxanone (PDO) filler compared to poly-L-lactic acid (PLLA), polycaprolactone (PCL), and hyaluronic acid (HA) fillers. In both mouse and human skin models, a novel collagen stimulation was compared with hyaluronic acid filler. Materials and Methods: An electron microscope was used to capture images of the solid particle microsphere shape. Moreover, animal models named SKH1-Hrhr were used to assess the 12-week persistence of PDO, PLLA, or PCL filler. H&E and Sirus Red staining were used to compare collagen density. Five participants in the clinical trial received three injections in the dermis over an eight-month period. Skin density, wrinkles, and gloss were evaluated using DUB® skin scanner, Antera 3D CS, Mark-Vu, and Skin gloss meter after injection to assess the efficacy of fillers. Results: PDO microspheres had uneven surfaces and were spherical and consistent in size. In comparison to other fillers, the PDO filler demonstrated complete biodegradability in just 12 weeks and better neocollagenesis, and a lower inflammatory response than the HA filler. After three injections, the human body assay showed a significant improvement in skin gloss, wrinkles, and density. Conclusion: In comparison to PCL and PLLA, PDO filler demonstrated a comparable volume increase rate and better biodegradability. Furthermore, although its physical characteristics are similar to those of a solid, PDO has the advantage of being more organically spread. In photoaging mice, PDO fillers are thought to offer equivalent or superior anti-wrinkle and anti-aging effects to PBS, PCL, and PLLA.*

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Key Words: Polydioxanone, polycaprolactone, poly-L-lactic acid.

The formation of wrinkles, a characteristic sign of aging, is associated with reduced elasticity and thickness of the skin, lower bone density and loss of soft tissue volume because bones and skin share the same protein. The clinical characteristics of intrinsic skin aging are relatively minor, including fine wrinkles, dryness, and decreased elasticity. The extrinsic factors in skin aging include UV rays, smoking, climate (humidity, wind, and cold), skin irritation caused by soap and cosmetics, and the work environment. The intrinsic factors of skin aging include blood circulation disorders, genetic predisposition, poor nutrition, and stress. Reactive oxygen species (ROS) produced by ultraviolet rays activate various signal transduction pathways within skin cells. ROS become a main cause of photoaging by increasing the levels of proteases such as matrix metalloproteases (MMPs), reducing collagen production and elastic fibre synthesis, and producing skin wrinkles (1). Since 2000s, dermal filler products that improve wrinkles and replenish skin tissues by injecting safe materials into the facial dermis layer have been actively developed. Inserting sutures or injecting collagen-producing fillers for rejuvenation purposes

Table I. *Clinical trials*.

Male	Female	Averaged age
1	4	45.00±4.64
Numbering	**Sexual selection**	**Age**
1	Female	50
2	Female	45
3	Female	49
4	Male	39
5	Female	42

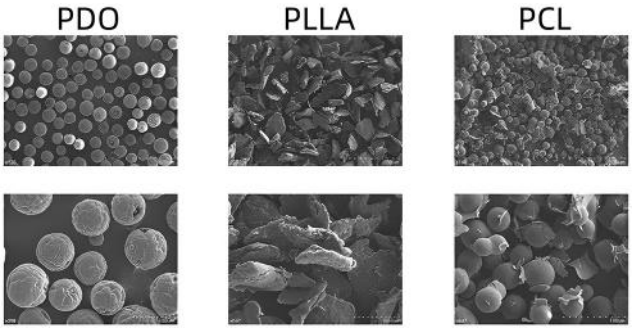

Figure 1. *Particle morphology of fillers*.

has become widespread recently. Dermal fillers are gel-like substances that are injected beneath the skin to restore lost volume, smooth lines, and soften creases, or enhance facial contours. It is a medical device that does not have any pharmacological action. Dermal filler can be classified according to the properties and residence time of the raw materials into absorbable and non-absorbable, depending on whether they are absorbed *in vivo*. There are two main ways by which tissue fillers function. The first is by filling spaces in the skin to augment volume. The second is by stimulating the surrounding skin tissue to synthesize new collagen. The former shows greater improvement post-procedure, with the effect diminishing over time. In contrast, collagen synthesis fillers initially show a minor improvement in wrinkles but, over time, induce the synthesis or regeneration of collagen and other connective tissues to create spaces and scaffolds for fibroblasts or vascular cells to enter, resulting in greater effectiveness during the later rather than the earlier stages (2, 3).

Biodegradable or bioabsorbable polymer is a polymer that is decomposed and destroyed by simple hydrolysis or the action of enzymes. Recently, polydioxanone (PDO) is increasingly used for wrinkle reduction with multiple applications of single biodegradable thread coated with PDO in various areas of the face. Although previous reports have demonstrated the efficacy of PDO threads, a filler made of PDO has not been developed for volume augmentation or anti-wrinkle purposes (4). The present study evaluated a PDO filler in comparison to the existing commercial products PCL, PLLA and HA fillers. In addition, PDO fillers were applied in 5 adult men and women aged 30 to 50 years and measured by quantifying true pitch density, skin wrinkles, and skin glow.

Materials and Methods

Materials. PDO (Polydioxanone, ULTRACOL®, Ultra V Co., Ltd., Seoul, Republic of Korea), PLLA (Poly-L-lactic acid, Sculptra®, Galderma Laboratories, Nestlé SA, Zug, Switzerland), PCL (Polycaprolactone, ElansémM®, Sinclair Pharma, Irvine, CA, USA) and hyaluronic acid (Re-stylane®) fillers were used. PDO filler was composed of PDO and sodium carboxyme-thyl cellulose (CMC). This PDO filler was approved by the KOREA Food and Drug and Administration (KFDA) and was given a CE certificate in 2021. Rat CXC2/IL-8 antibody (cat: MAB8110) was obtained from R&D System (Minneapolis, MN, USA). Anti-CD68 antibody (cat:125212) was obtained from Abcam company (Cambridge, UK). Alex Fluor 488 rabbit anti-mouse IgG (H+L) (cat: A27023) was purchased from Invitrogen (Carlsbad, CA, USA).

Particle morphology. Three different fillers were washed with 30% ethanol and then desiccated in an oven for 48 h. Filler particle morphology was evaluated by field emission scanning electron microscopy (FE-SEM; LEO SUPRA 55, Carl Zeiss, Germany). The HA Filler was prepared in a syringe of 1 cc.

Animal experiment. All animal experiments were approved by the Institutional Animal Care and Use Committee of Chung-Ang University College of Medicine (approval No. 16-00069). Seven-week-old female hairless mice (SKH1-Hrhr; Saeron Bio Inc, Seoul, Republic of Korea) were raised in a facility with controlled temperature (24±2˚C), relative humidity (50±10%), and light (12 h light/12 h darkness, without any ultraviolet emission). There was a stabilization period of at least one week for acclimatization prior to the experiment.

Safety and biocompatibility test; PrimosLITE Topography. A total of 24 mice were randomly divided into three groups: Group 1, PDO filler; Group 2, PLLA filler; and Group 3, PCL filler. Filler (100 μl) was injected into the central dorsal skin of hairless mice (1 cm from the tail) after anesthetization with zoletil and rompun. To evaluate the durability of filler, three-dimensional (3D) images were obtained at 0, 3 days and 1, 4, 8, 12 weeks after injection using Folliscope (LeedM, Seoul, Republic of Korea) and PRIMOS (GFMesstechnik GmbH, Teltow, Germany).

PRIMOS 5.6 software was used to conduct the analysis. PRIMOS is a non-contact optical three-dimensional skin imaging and measurement system that measures the degree of wrinkles and changes in the texture, *etc*., of living skin. The strip projection technique is used to quickly and accurately measure and record multiple parameters about the skin, including its roughness, volume, wrinkles, wound size, *etc*. To induce photoaging wrinkles on the backs of the experimental animals, they were exposed to UV A and

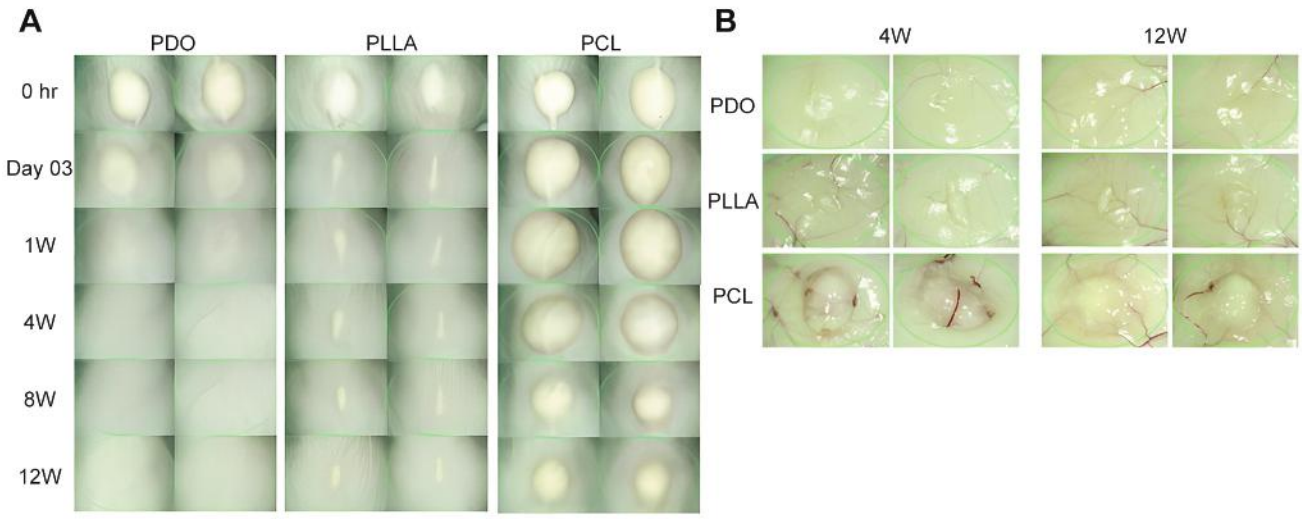

Figure 2. *Images of the skin after in vivo administration. (A) Surface of the skin following in vivo administration of the fillers. (B) Images of the skin at 4 and 12 weeks after in vivo administration. Images were obtained using Folliscope (LeedM, Seoul, Republic of Korea) at a magnification of 15×.*

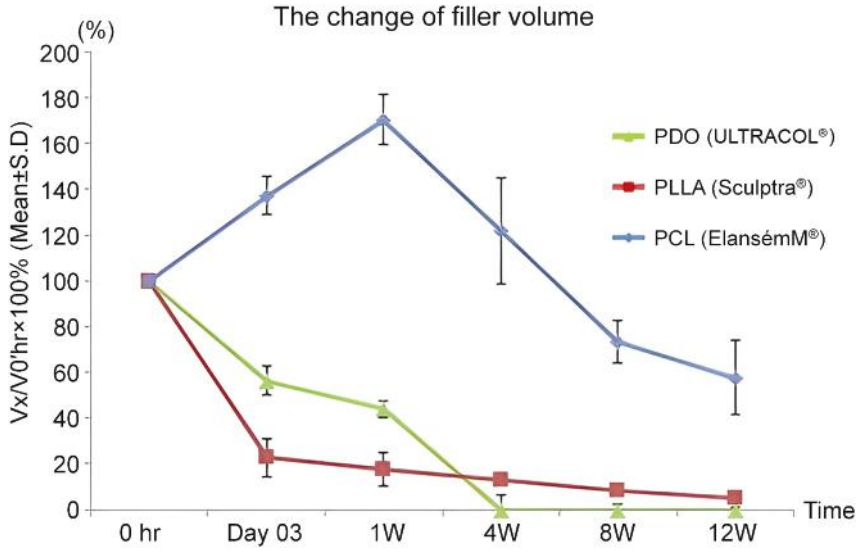

Figure 3. *The evaluation of filler's durability. Analysis of changes in filler volume. Data were obtained by using Primos-LITE Topography (with Software PRIMOS 5.6, Tests of Normality; Shapiro-Wilk, Test of Homogeneity of Variances; Levene Statistic).*

B radiation three times a week using BIO-SPECTRA (Vilber Lourmat, Marne-la-Vallée, France).

Histological evaluation – Collagen concentration. The experimental animals were anesthetized (ketamine:rompun=4:1) and the PDO or HA fillers were injected into the back of the mice. Each evaluation was conducted according to the following schedule, and at least 27 animals were used per group. All fillers were subcutaneously injected in consistent 200 μl volumes, and the animals were observed immediately after the injection to check for sample leakage. The change in collagen concentration were examined on the operation day and after 1, 2, 3, 4, 5, and 6 months. The experimental animals were sacrificed and skin tissue obtained from the filler injection site and a non-injected site were fixed in a 10% neutral buffered formalin solution. The tissues were then embedded in paraffin, sectioned to 5 μm, and examined for host response following haematoxylin and eosin staining. Collagen concentration was examined using Sirus Red staining. The skin tissue compatibility of the injected samples was evaluated by checking for an inflammatory response, a major criterion. After observing the tissue slides using an optical microscope, the change of collagen concentration was measured.

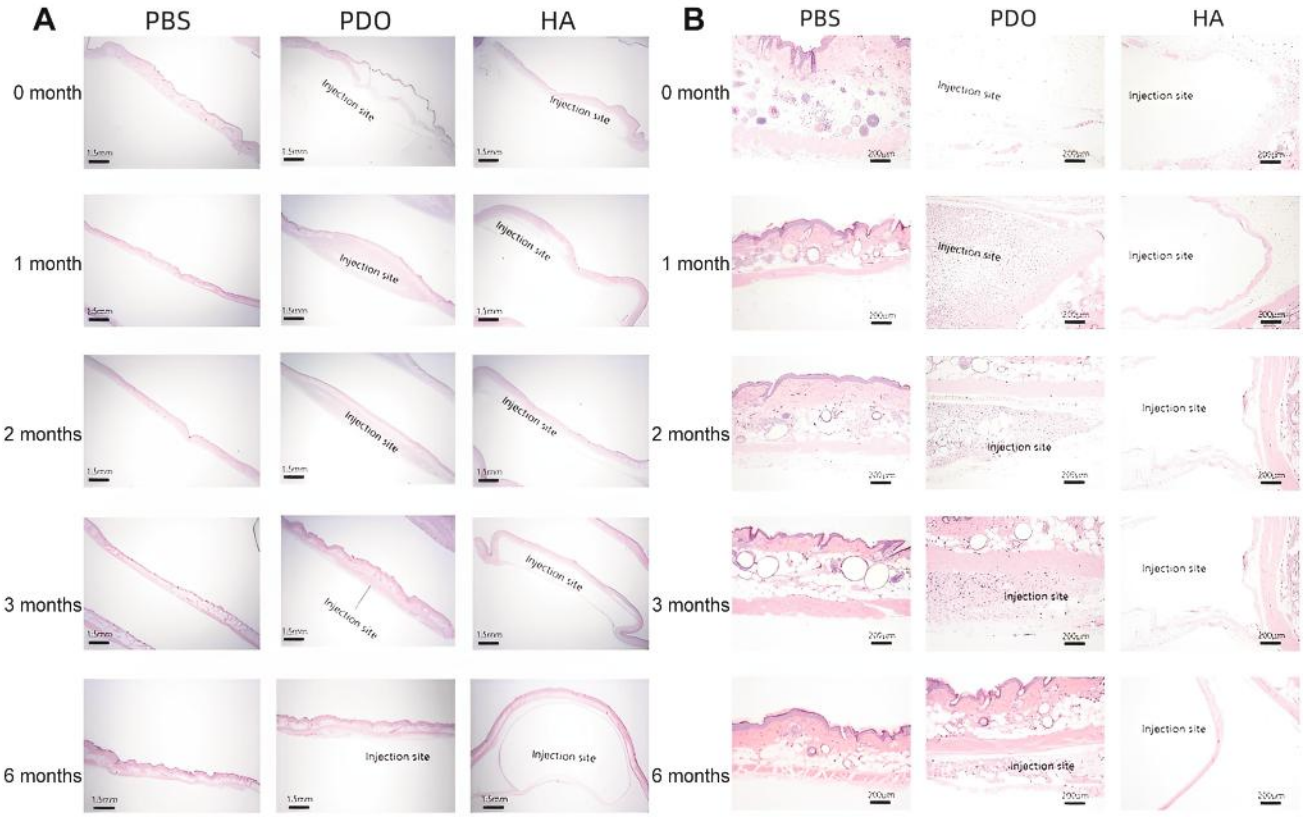

Figure 4. *Changes of (A) epidermal thickness (original magnification of 12.6×) and (B) dermal collagen fibres (original magnification of 100×).*

Statistics measurements. Quantitative measurement data were analysed for trends using a table summarizing the period, group names, means and standard errors of the mean (mean±SEM) and improvement rate. The control and experimental groups were compared by using statistical tests. Statistical tests (*e.g.*, Shapiro-Wilk test for normality, Kruskal-Wallis test for *p*-values and one-way ANOVA) were performed by using SPSS 18 program. A *p*-value of less than 0.05 was construed as indicating a significant difference between groups. The Mann-Whitney test and independent *t*-tests were used to compare groups.

In human body assay for skin improvement. Skin Density was measured using DUB® skin scanner (EOTECH SA, Marcoussis, France) that analysed the absolute density of the dermis by applying high resolution ultrasonic waves. Increasing numbers indicate improvement of the dermis density. In addition, skin wrinkles were measured using Antera 3D CS (Miravex Limited, Dublin, Ireland) at various wavelengths. In this case, decreasing numbers indicate improvement of skin wrinkles. Skin gloss was measured using Mark-Vu (PSI Plus Co., Ltd., Suwon, Republic of Korea) and Skin gloss meter (Delfin Technologies, Kuopio, Finland). The above assays for evaluating skin improvement were done at KCAC (Korea Clinical trial Analysis Center) to test the PDO filler of 100 mg diluted by water for injection (WFI). We performed evaluation tests before the injection of the PDO, after three injections (2 weeks intervals), and after eight months. The lectotype and exceptional specifications of the fillers followed the provisions of clinical trials specified in the KFDA (Table I).

Results

In vitro test. Particles of the PDO filler were uniformly sized with spherical shape and an irregular surface. PLLA microspheres were very rough, non-uniform sized, and flat with a pointed shape. PCL microspheres were smooth and uniformly sized spherical particles (Figure 1).

In vivo test: Safety & biocompatibility test. The shape preservation, migration, and volume change of the administered samples were evaluated using the PRIMOSLITE (GFMesstechnik GmbH) and Folliscope (LeedM) instruments immediately following administration (0 h), on day 3, and at 1, 4, 8, and 12 weeks. Magnified images obtained using a folliscope were used to examine the shape and degree of leakage of the samples upon *in vivo* administration (Figure 2 and Figure 3). In the first week, a dramatic increase in the volume of PCL was observed, whereas that of the other two groups reduced. PDO and PLLA almost degraded at 4 weeks and 12 weeks, respectively, after administration. However, the volume of PCL was about three-fifths compared to the original volume. PRIMOS data also suggested an increase of approximately 1.6-fold in week one relative to the initial volume, followed by a gradual decrease. PLLA showed a sudden decrease in volume of approximately 0.23-fold on day 3, followed by

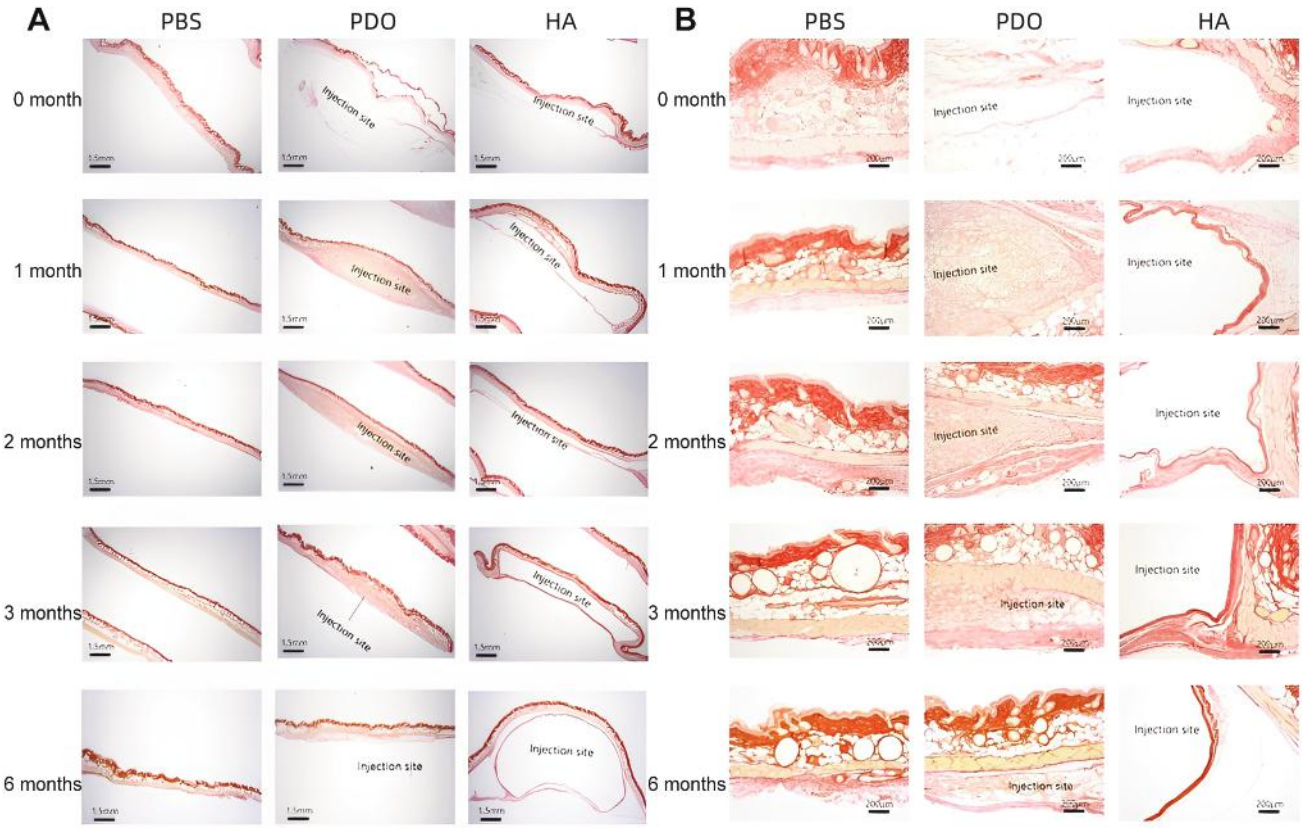

Figure 5. *The Sirius red positive area indicating collagen deposition around the filler (original magnification of 100×).*

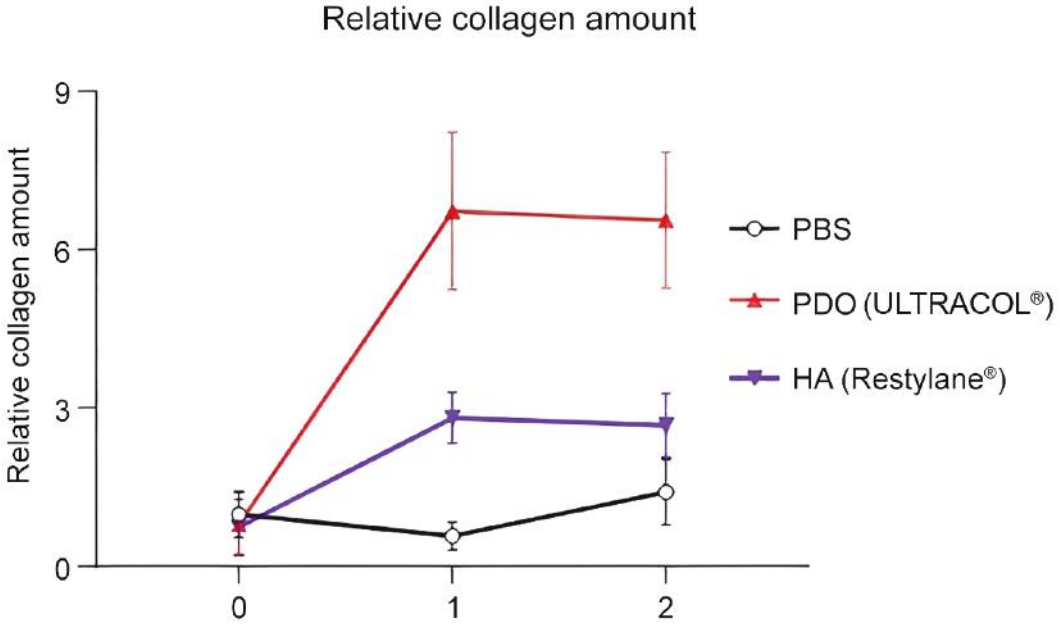

Figure 6. *Analysis of Sirius red positive area indicating collagen deposition around the filler.*

Table II. *Improvement rate (%) of PDO filler for dermal density, wrinkles, and skin radiance improvement.*

Measurement items	Measure viewpoint	AVE±S.D.	Improvement rate (%)
Electronic intimacy (%)	Before injection	11.04±2.79	–
	After 3 treatments	14.72±4.93	▲34.36
	8 months after injection	13.69±3.85	▲23.23
Wrinkle index (A.U.)	Before injection	38.59±8.05	–
	After 3 treatments	33.14±6.18	▼13.33
	8 months after injection	34.59±4.49	▼8.64
Skin radiance (SGU)	Before injection	55.67±3.10	–
	After 3 treatments	60.80±7.22	▲9.15
	8 months after injection	57.20±4.89	▲2.97

Improvement rate(%)=(After-Before)/Before×100.

a gradual and continuous reduction until week 12. PDO also exhibited a decrease in volume of approximately 0.2-fold on day 3. Visual observation at week four was difficult and PRIMOS measurements were not conducted. A significant between-group difference was found from week 0 to week one. From week four to week 12, when the volume of PDO was not determined, a significant between-group difference was observed between PCL and PLLA (One-way ANOVA p=0.000). Thus, PDO is expected to have better biodegradability than other biodegradable control polymer fillers. It is believed to offer the advantages of diffusing naturally without massaging, as shown in the photographs of dissected tissue.

We performed research to confirm new collagen formation by foreign body reaction to PDO filler compared to HA filler. For research on new collagen formation, we checked that initial well. One month after subcutaneous injection of PDO and HA fillers, a slightly different pattern of tissue reaction was observed depending on the filler, and foreign body reaction accompanied by multiple macrophage infiltration and fibrosis was observed following injection of the PDO filler. Furthermore, collagen formation around microparticles of the PDO filler without dense agglomeration confirmed that PDO fillers were distributed uniformly in the tissue 3 months after injection. However, in the case of the HA filler, a thin film made of fibrous connective tissue was formed around the injection site only, and inflammatory cell infiltration was not observed. In addition, in the case of the HA filler, collagen was formed thinly around the injection site only. Even after three months, collagen was only thinly present around the HA filler. The PDO filler area was gradually reduced as biodegradation progressed for a period of 2-3 months, which was accompanied by amelioration of inflammation and a decrease in the number of related cells. Finally, because the degradation of fine particles of the PDO filler proceeded, the initially injected fine particles were hardly observed after three months. However, because biodegradation did not proceed, the HA filler was maintained at the initial injection state even after three months (Figure 4).

We compared quantitative measurement results of collagen generated following injection of the fillers or PBS at zero months using the Sirius red positive area (collagen) value. After one month, collagen formation induced by PDO filler injection was 6.75 times higher than that of PBS injection. In addition, the PDO filler induced the production of 2.45 times higher collagen than the HA filler. After two months, the collagen amount at the PDO filler injection site decreased by 2.5% compared to the average value after one month. In the case of the HA filler, there was no change in the collagen amount compared to after 1~2 months. However, 3~6 months after administration a similar decrease in the collagen amount was observed at the site of the injection of both fillers (Figure 5 and Figure 6).

Improvement of dermal density, wrinkles, and skin radiance following injection of the PDO filler. The human application test was conducted at the KCAC using the PDO filler on five adult males and females aged 30 to 50 years who met the selection criteria. The images of the dermis were taken by a DUB® skin scanner (EOTECH SA) and analysed for absolute density. Increased values indicate increased dermal density (improves). Skin wrinkles were measured by irradiating various wavelengths through Antera 3D CS (Miravex Limited); decreased wrinkle index values indicate improved wrinkles. The skin luminosity was measured using the specular light mode with Mark-Vu (PSI Plus Co., Ltd.). In addition, the Skin gloss meter (Delfin Technologies) quantified the degree of reflection of the skin through a laser; increased values indicate increased radiance (improves). For PDO filler, the finished product (UltraV ULTRACOL® 100) was sufficiently diluted with 4cc of sterile injunction water and injected into the subject. After three treatments, dermal density was improved by 34.36%, skin wrinkles were improved by 13.33%, and skin radiance was improved by 9.15%. After eight months of operation, the improvement effect was reduced in all test items (Table II, Figure 7).

After PDO filler was administered to the test subject, images of the dermis were taken by DUB® skin scanner (EOTECH SA) and the absolute dermal density was determined. It was improved by 34.36% compared to that before the procedure, from 11.04±2.79 to 14.72±4.93. In addition, eight months after the procedure, dermal density was 13.69±3.85, which corresponded to a 23.23% improvement, confirming that the dermal density was effectively maintained using the PDO filler (Figure 8).

After the PDO filler was applied to the test subjects, the skin wrinkles were measured at various wavelengths using Antera 3D CS (Miravex Limited). After the procedure, wrinkles were 33.14±6.18, which corresponded to 13.33% improvement compared to that before the procedure. In addition, eight months after the procedure, wrinkles were 34.59±4.49, which corresponded to 8.64% improvement (Figure 9).

Figure 7. *Improvement of dermal density, wrinkles, and skin radiance of PDO filler.*

After PDO filler was administered to the test subjects, skin luminosity was measured using Mark-Vu (PSI Plus Co., Ltd.) and Skin gloss meter (Delfin Technologies). It was 55.67±3.10 before treatment and 60.80±7.22 after 3 treatments. This corresponds to 9.15% improvement compared to before the treatment. In addition, eight months after the procedure, it was 57.20±4.89, which corresponds to 2.97% improvement (Figure 10).

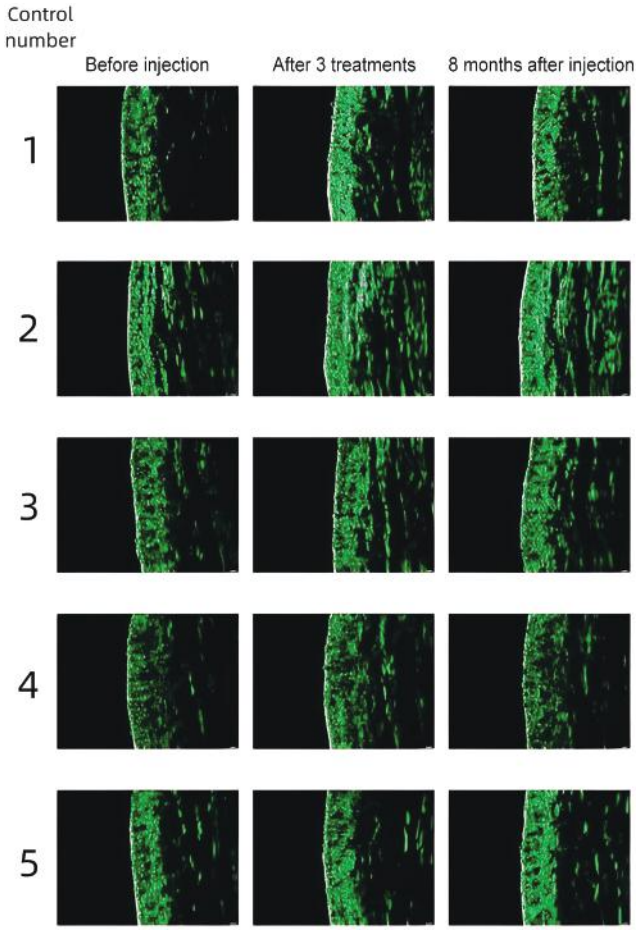

Figure 8. *Images of dermal density taken using a DUB® skin scanner (EOTECH SA).*

Discussion

PDO is a completely biodegradable ester-linked polymer. During the past 50 years, PDO has been used as a surgery thread without any side effects on the human body. Previous PDO research was only on the mouse photoaging model. Based on that, we studied the actual collagen regeneration and skin improvement induced by PDO to research for the biophysical characteristics, safety, and efficacy of the PDO filler compared with PLLA and PCL fillers. We also investigated new collagen formation in comparison with the HA filler. PDO is a crystalline, biodegradable polymer that chemically consists of multiple repeating ether-ester units. It is obtained by ring-opening polymerization of the p-dioxanone monomer. It is characterized by a glass transition temperature in the range of –10 and 0˚C and a crystallinity of 55%. PDO is used biomedically in various fields, such as orthopaedic surgery, plastic surgery, drug delivery, and cardiovascular and

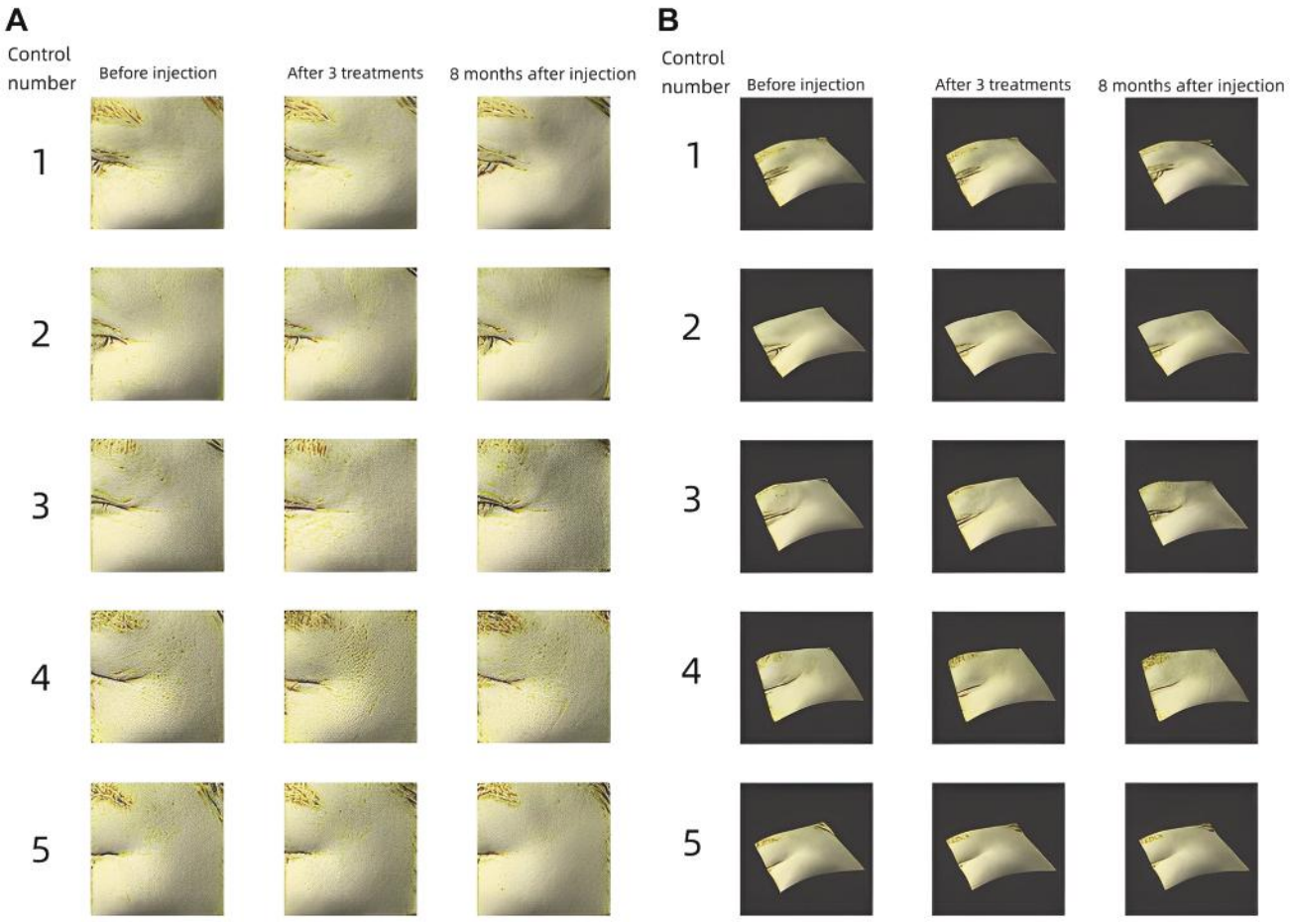

Figure 9. *Images taken by using Antera 3D CS (Miravex Limited) showing changes in wrinkles on the face (A) and the canthus skin (B).*

tissue engineering. This polymer is degraded by hydrolysis and excreted from the body (1, 5). As a biodegradable polymer commercialized in the 1990s, PDO has a lower melting point and low mechanical strength compared to other biodegradable polymers with a retention period of 12 weeks in the body. Short-term exposure of blood to PDO threads did not disturb the function of macrophages and white blood cells (6). A two-component suture made of PDO and copolymer was completely absorbed within six months after implantation in rats, and no particular tissue or foreign body reaction was observed during the degradation process (7). Studies on the safety of polydioxanone have been conducted in various pre-clinical and clinical studies *in-vitro* or in humans as implant products including sutures and stents. According to a related study, PDO-based polymer materials are completely absorbed after 10 to 12 weeks (around three months) *in vitro*, 15 to 16 weeks (around four months) *in vivo*, and completely absorbed within six to seven months in the human body (2, 3, 8-10). In this study, PDO volume was analyzed using PRIMOSLITE Topography after injection *in vivo* for safety, persistence, and biodegradability evaluation, and we found that the volume gradually decreased as it was naturally absorbed into skin tissue over time. After injection in tissue, mild inflammation and about 99.2% biodegradability were observed after 18 weeks of filler injection in the tissue. This result is similar to HA filler (11, 12). PDO is expected to be maintained for about six months when applied to the human body according to its biodegradation and decomposition time *in vivo* (2, 3). As a kind of dermal filler, PDO microspheres showed a uniform size and spherical shape. This research showed that PDO fillers stimulate the synthesis of new collagen. In addition, PDO particles were found to remain in their original position for 12 weeks after injection. After injecting PDO filler, the CMC gel carrier is absorbed by macrophages slowly for several weeks. PDO microspheres stimulate neocollagenesis to replace the volume of absorbed CMC gel (13, 14). A characteristic of PDO-based fillers is that they have a bio-stimulating effect instead of an immediate direct peeling effect. The collagen stimulating filler improved wrinkles slightly at first. However, these fillers induce the synthesis or

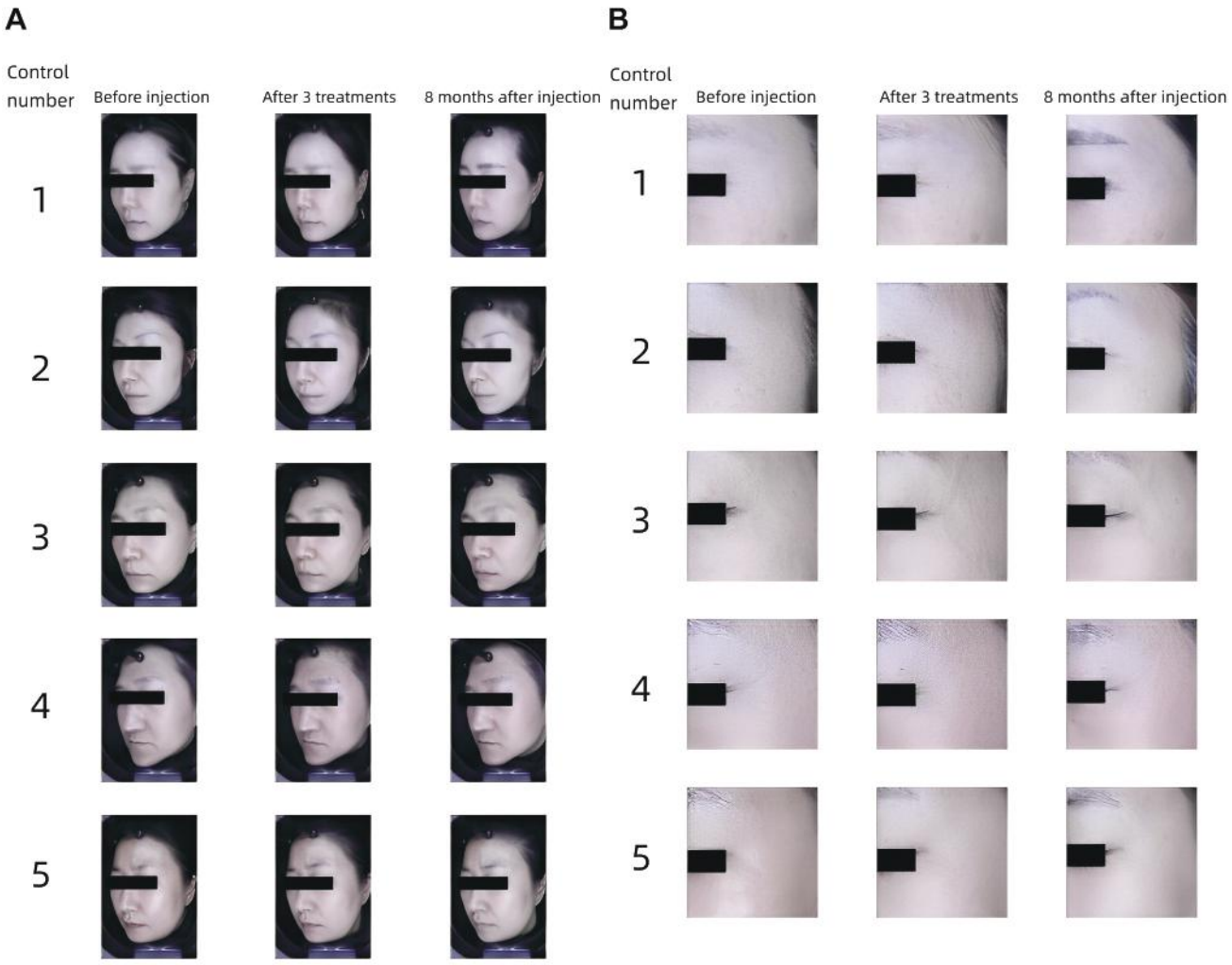

Figure 10. *The evaluation of skin gloss. Images taken by using Mark-Vu (PSI Plus Co., Ltd.) showing changes in skin radiance on the face (A) and the canthus skin (B).*

regeneration of collagen and other connective tissue over time. Therefore, because PDO creates space and scaffold for fibroblasts or blood vessels, it has a great effect than other fillers. Therefore, PDO fillers are suitable for individuals who want gradual improvement. We can recognize that PDO fillers stimulate collagen similar to PLLA and PCL fillers. In addition, we confirmed that the PDO filler has excellent in biodegradability properties, particularly compared to other fillers. Skin surface roughness was reduced significantly after injecting PDO filler. We confirmed that dermal density was improved by 34.36%, skin wrinkles were improved by 13.33%, and skin radiance was improved by 9.15% after 3 treatments with the PDO filler in the clinical study. The improvement effect decreased in all clinical tests after 8 months of treatment. Since PDO filler has secured safety due to its effective biodegradation properties, it could be an attractive choice for natural volume reduction correction and restoration of photoaging skin.

Conclusion

In conclusion, The PDO filler has a similar initial volume enhancement rate and better biodegradability compared to the existing commercial products PCL and PLLA. Moreover, although its physical properties are close to those of solids, it offers the advantage of spreading out more naturally compared to the control polymers. When evaluated in comparison to PBS, PCL, and PLLA in photoaged mice, the PDO filler had similar or better anti-wrinkle and anti-aging effects. We confirmed that dermal density was improved by 34.36%, skin wrinkles were improved by 13.33%, and skin radiance was improved by 9.15% after three treatments with

the PDO filler in the clinical study. The improvement effect decreased in all clinical tests after eight months of treatment. PDO filler is safe and best choice for neocollagenesis to correct volume loss and provide skin improvement.

Conflicts of Interest

The Authors declare that they have no competing interests in relation to this study.

Authors' Contributions

Shu-Yi Zhou, So Min Kang, Yeon Ju Gu, Xin Rui Zhang, Dong Keon Yon, Chan-Yeong Heo: conceptualization, methodology, writing original draft and editing. Byung Ho Shin, Jung Ryul Ham, Won Ku Lee, Je Geun Jeong, Han Jin Kwon: software, visualization. Chan-Yeong Heo: supervision, validation, project administration.

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