Received: 6 August 2023 | Revised: 18 October 2023 | Accepted: 3 November 2023

DOI: 10.1111/jocd.16085

JCD Journal of Cosmetic Dermatology WILEY

ORIGINAL ARTICLE

Skin rejuvenation effect of the combined PDLLA and non cross-linked hyaluronic acid: A preliminary study

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Funding information
VAIM Co., LTD

Abstract

Background: Skin aging is characterized by wrinkles, rough skin texture, pigmentation, facial erythema, and telangiectasia through structural and functional changes in the epidermis and dermis. Recently, injectable poly(D, L-lactic acid), a biodegradable polymer, has been used widely for skin rejuvenation.

Aims: This study aims to assess the efficacy and safety of injectable dermal poly D, L-lactic acid) for skin rejuvenation.

Patients/Methods: A total of 16 patients who desired skin rejuvenation were included. All participants received two or three procedure sessions with a 4 weeks interval between sessions. Clinical and three-dimensional images at baseline, before each procedural session, and follow-up visits were obtained. Therapeutic effects were assessed by evaluating signs of aging skin and overall improvement by dermatologists and patients. Histologic examinations with special stains were performed on the posterior auricular areas of consenting patients at baseline and follow-up visits after injecting poly D L-lactic acid into the postauricular area as in the face.

Results: Overall, statistically significant differences were observed in all signs of aging skin, such as fine wrinkles, skin texture, irregular pigmentation, telangiectasia, and facial erythema before and after treatments. Half (50%) of patients responded that there was more than 50% overall improvement. There were no severe adverse events. Histologic examination demonstrated increases in collagen and elastic fibers in the dermis.

Conclusions: Results of this preliminary study suggest that injectable dermal poly D, L-lactic acid can significantly affect skin rejuvenation without causing any serious adverse events.

KEYWORDS
L-lactic acid, poly D, skin booster, skin rejuvenation

1 | INTRODUCTION

The rise in life expectancy has resulted in a significant increase in patients complaining about skin aging, leading to an increased demand for skin rejuvenation. Photoaging, known as extrinsic aging, is caused by external factors such as ultraviolet irradiation.[1] Collagen degradation can occur due to UV radiation and non-UV solar irradiation with the production of reactive oxygen species (ROS), proinflammatory cytokines, and matrix metalloproteinase (MMP).[2,3] These molecular and biological changes manifest visibly as alterations in wrinkles, pigmentations, abnormal skin texture, volume loss, and epidermal and dermal thinning. Various approaches have been developed to improve skin aging, including topical agents, chemical peeling, dermabrasion, laser skin resurfacing, and dermal filler injection.[4,5]

Interest in dermal fillers and skin boosters has been growing as they can help even out, correct soft tissue volume, and contribute to skin rejuvenation.[6–9] Several injectable skin boosters can be used, including HA (hyaluronic acid), biodegradable collagen stimulators, and nonbiodegradable products. Poly-L-lactic acid (PLLA), poly-D, and L-lactic acid (PDLLA), belonging to the category of biodegradable collagen stimulators, have been increasingly utilized in recent years.[10,11] Because of their biodegradable and biocompatible features, these poly-lactic acid (PLA) materials have already been used as various surgical materials, including suture threads, nails, pins, and screws.[12]

Oh et al.[11] have reported that PDLLA can induce increased M2 macrophage polarization and interleukin (IL)-10 expression in senescent macrophage and aged animal skin. These changes can reduce adipose tissue-derived stem cells (ASCs) senescence and increase their proliferation. Additionally, they have reported that PDLLA contributes to skin rejuvenation by lowering the expression of NF-kB and MMP2/3/9.[11]

There is no study on injectable PDLLA targeting the entire face. However, one study on lower eyelid rejuvenation and case reports has shown a skin rejuvenation effect of PDLLA.[13,14] The present study aimed to assess the efficacy and safety of injectable PDLLA in participants with skin aging changes.

2 | MATERIALS AND METHODS

2.1 | Patients

Sixteen patients (15 women and 1 man) who desired skin rejuvenation were treated at our Department of Dermatology between March 2022 and February 2023. The protocol of this study was approved by the Institutional Review Board (IRB) of our institution. All participants were informed about the potential benefits and risks of the procedure and provided written informed consent before treatment.

2.2 | Inclusion and exclusion criteria

This study was conducted on healthy adults aged 20–65 who desire skin rejuvenation. Patients with a history of keloid, active cutaneous infections, hyaluronic acid hypersensitivity, or uncontrolled general disease were excluded from this study. Individuals who had undergone a laser, chemical peel, or botulinum toxin treatment within the past 6 months, facial plastic surgery within 12 months, or filler procedure within 24 months were also excluded. Pregnant or lactating patients were also excluded from this study.

2.3 | PDLLA preparation

PDLLA/HA (PDLLA 42.5 mg + HA 7.5 mg; Juvelook, VAIM co. LTD.) was dissolved in 10 mL mixture of HA (Aragan injection (prefilled), DongKwang co. LTD; 2.5 mL), 1% lidocaine hydrochloride hydrate (2.5 mL), and normal saline (5 mL) mixture at a 1:1:2 ratio.

2.4 | Protocol

All participants received two or three procedural sessions with a 4-week interval between sessions. One dermatologist performed treatment for all patients. The protocol of this study is summarized in Figure 1. Before each treatment session, a topical anesthetic (eutectic mixture of 2.5% lidocaine HCl and 2.5% prilocaine; Taiguk Pharm Co., Ltd.) was applied to the cleaned face for 40 min to reduce pain. After that, 4 mL of diluted PDLLA mixture was injected into the upper dermis of the face (forehead, temple, cheek, chin, nose, and posterior auricular area) using an autosensing mesotherapy injector (Dermashine®, Huons meditech co. LTD.) through 32 gauzes nine pin needles (Figure 2; Video S1). This injector device had a press-sensitive automatic injection system, which could reduce drug loss and facilitate consistently accurate injection. For each session, 140 shots were injected with a fast flow rate, an auto-dose injector mode (one dose was approximately 0.0286 mL), and a power level of 2.

Additionally, PDLLA was injected into both sides of the postauricular region in all sessions for patients who initially consented to histologic evaluation. Of the 16 participants, 14 were treated with two sessions and 2 with three. The two participants were treated with three sessions because they were not satisfied after two sessions. Follow-up visits were made 16 weeks after the final session for patients who completed the procedure in two sessions. For patients who completed the procedure in three sessions, a follow-up visit at 12 weeks after the final procedural session was set.

2.5 | Clinical assessment

We obtained clinical photographs and three-dimensional (3D) images at baseline, before each procedural session, and at follow-up visits (16 weeks or 12 weeks after the final treatment). Clinical photographs were obtained using a digital camera (EOS 80D; Canon KK). 3D photographs were captured using a 3D camera (LifeViz® Infinity; QuantifiCare, Biot, France) and the stitch program. The photo was taken in the same position with the same light exposure of the photo room for all patients. Clinical photographs were taken

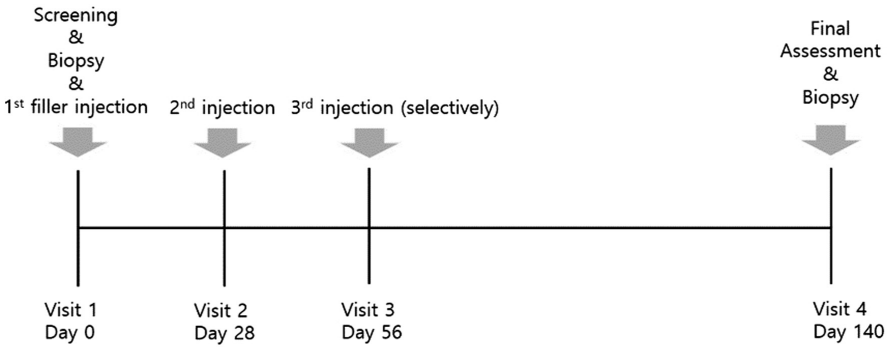

FIGURE 1 Study design and visit schedule.

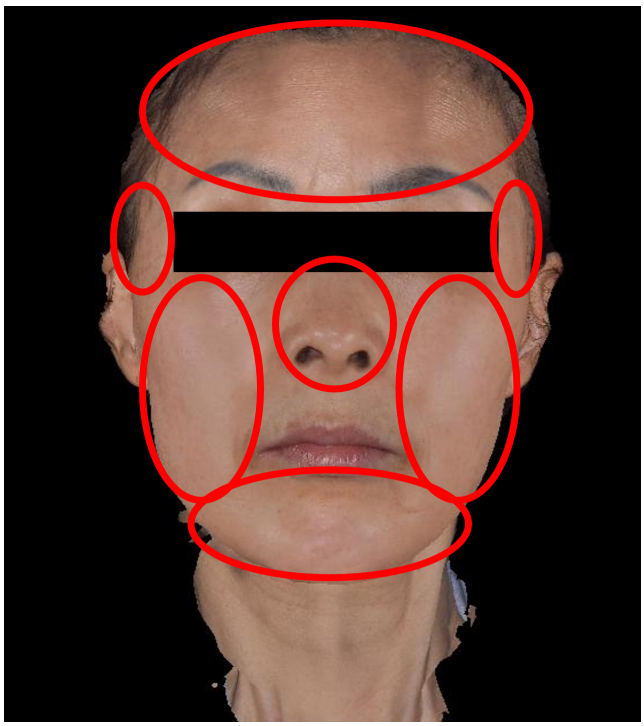

FIGURE 2 Using a mesotherapy injector, we injected a PDLLA mixture into the upper dermis of the face, including the forehead, temples, cheeks, chin, nose, and posterior auricular area. The space within the red ovals indicates the areas where we performed the procedure.

with the patient's eye closed under appropriate lighting conditions. In contrast, 3D photographs were taken with the patient's eye open using the 3D camera's built-in flash with lighting turned off.

Therapeutic effects were evaluated by measuring five aging skin signs using a 10-point scale (0 point being nonexistent and 10 point being considered a pathological condition) by two dermatologists who did not participate in the treatment before the first treatment session and at follow-up visits. All evaluations were randomized after taking photographs of all patients to allow for blind estimation. These five signs were fine wrinkles, skin texture, irregular pigmentation, telangiectasia, and facial erythema. At follow-up visits, patients were also asked about their overall improvement. The following scoring scales were used to determine the degree of overall improvement.

Scoring scales:

1. No improvement
2. 1%–24% improvement
3. 25%–49% improvement
4. 50%–74% improvement
5. 75%–100% improvement

Any adverse events that had occurred since the previous session visit were identified during treatment session visits and follow-up visits.

2.6 | Histopathological examination

Histologic examination was conducted with the participant's consent. Punch biopsies with a diameter of 2 mm were obtained from one side of the posterior auricular area in a randomized direction before the first treatment session and from the opposite side of the posterior auricular area at the follow-up visit. Specimens were examined by hematoxylin & eosin (H&E) staining, elastin van Gieson (EVG), and Masson's trichrome (MT) staining.

2.7 | Statistical analysis

Demographic data, adverse events, and overall improvement underwent descriptive statistical analysis, while the scales of skin aging signs were compared using the Wilcoxon signed rank test. All statistical analyses were conducted using SPSS version 25 statistical software. A p-value <0.05 was considered to mean statistical significance.

3 | RESULTS

A total of 16 patients completed the study protocol and questionnaires. The participants in the study were all Asian. Demographic data of all participants are presented in Table 1. Only one patient was a man with Fitzpatrick skin type (FST) IV. The others were women with FST III and IV. Their average age was 50.6 years (range

33–62 years). Although the participants did not have any procedures in recent months, they exhibited a range of skincare product usage, including sunscreen, whitening cream, and others, from none to regular usage.

Results of comparative analysis of aging skin signs such as fine wrinkles, skin texture, irregular pigmentation, telangiectasia, and facial erythema before and after treatment sessions are shown in Table 2. Overall, statistical significance was observed in all subitems of aging before and after the treatments. Table 3 shows the overall improvement of patients' surveys. Eight (50%) patients responded that there was an overall improvement of more than 50%.

According to 3D photographs, skin aging signs improved in the abovementioned characteristics (Figures 3 and 4). PDLLA injection also showed a facial contouring effect (Figure 5). No serious adverse events were identified except temporary procedural pain and facial erythema (Table 4). The duration of temporary pain reported by the patients disappeared immediately after the procedure.

We performed biopsies on 11 out of 16 patients who consented to histological evaluation. Histopathological findings demonstrated an increase of collagen fibers within the dermis by MT staining (Figure 6). Elastic fibers in the dermis were increased and thickened with EVG staining (Figure 7). In addition, these histologic changes were more pronounced in the superficial dermis compared to the deep dermis.

TABLE 1 Demographic data of enrolled patients.

Characteristic	Value
Sex, *n* (%)	
Female	15 (93.8%)
Male	1 (6.3%)
Age, year	
Range	33–62
Mean (SD)	50.6 (7.7)
Fitzpatrick skin type, *n* (%)	
Type III	8 (50.0%)
Type IV	8 (50.0%)
Treatment session, *n* (%)	
2	14 (87.5%)
3	2 (12.5%)

4 | DISCUSSION

Aging skin generally shows wrinkles, sagging, and decreased elasticity, and these changes in the skin are due to the depletion of collagen, elastic fibers, and other proteins in the dermis. Depletion of hyaluronic acid (HA) can explain this phenomenon. Because HA can attract water hundreds of times its molecular weight, supplementing this ingredient to the dermis has skin rejuvenation effects.[15,16] Conventional HA filler injections that directly inject a relatively large amount of HA into deep wrinkles, such as nasolabial fold can have some adverse events, including vascular complications and allergic reactions.[17,18] Hydrolifting is a relatively recent technique for injecting a small amount of skin booster through several passes into a large area, such as the whole face. It possesses a minor volume-filling effect compared to conventional HA filler. However, it can exert a more profound impact on skin rejuvenation.[16]

PLLA, a biocompatible and biodegradable polymer, can break into lactic acid to stimulate collagen synthesis.[5,12] PLLA injection was approved for HIV-associated facial lipoatrophy in 2004.[19,20] PLLA exhibits a longer lasting effect than HA. Thus, PLLA requires fewer procedures than HA. However, injectable PLLA is known to induce local skin reaction and stimulate foreign body reaction, which can lead to M2 subtype macrophage polarization and recruitment of immune cells. With these reactions, PLLA-induced collagen synthesis, soft tissue augmentation, and skin thickening can occur by secreting various cytokines in vitro, in vivo, and animal studies.[5,12] Furthermore, there are several reports of late-onset granuloma formation after PLLA injection.[21]

PDLLA is also a chiral molecule of PLA. PDLLA and PLLA generate microspheres with distinct shapes, although they share the same chemical form.[11,19] PDLLA particles used in the present study are spherically shaped and empty inside because of their foamy feature. This means that PDLLA has a more significant volume-restoring effect because PDLLA occupies a larger volume than PLLA for the same weight.[11] It can be anticipated that PDLLA has a low likelihood of forming granuloma compared to other PLA-type particles. Additionally, a recent animal study has demonstrated that PDLLA can increase extracellular matrix by modulating macrophages and increasing adipose-derived stem cell proliferation.[11] Furthermore, it has been reported that PDLLA filler injection can treat acne scars using microneedle fractional radiofrequency in clinical practice.[20]

TABLE 2 Comparative analysis of skin aging signs.

	Average of scale		
	Pre-protocol	After-protocol	*p* value (95% CI)
Fine wrinkles	6.25	3.88	**0.001**
Skin texture	6.75	4.00	**0.001**
Irregular pigmentation	7.38	4.38	**0.001**
Telangiectasia	6.88	4.75	**0.003**
Facial erythema	6.75	5.00	**0.014**

Note: Data were analyzed using Wilcoxon signed-rank test. Values considered statistically significant ($p < 0.05$) are shown in bold.

The authors revealed that a microneedle fractional radiofrequency device could solve procedural pain caused by the injection of high-molecular weight substances and lead to more effective skin rejuvenation.[20] Although a radiofrequency device was not used in this study, we observed the effectiveness of injectable dermal PDLLA in skin rejuvenation among participants experiencing aging skin symptoms.

PDLLA particles act slowly as biodegradable collagen stimulators.[19] Therefore, we scheduled the follow-up visit 16 weeks after the second session. The soft tissue volume augmentation and maintenance effect of PDLLA can be described in two stages. The first stage is the volume increase caused by the PDLLA microsphere particles. The second stage is maintaining the volume by increasing the extracellular matrix, such as collagen, by macrophages and adipose-derived stem cells.[11,19] The second stage has been confirmed experimentally in aged animal skin up to 8 weeks and clinically in the nasolabial fold up to 6 months.[11,22]

This study found differences in treatment outcomes before and after injectable PDLLA injection, particularly in fine wrinkles, skin texture, and irregular pigmentation. There were relatively minimal differences in treatment outcomes of facial erythema and telangiectasia. In the context of improving uneven pigmentation, there are

TABLE 3 Overall improvement.

Grade of overall improvement	*N*, (%)
Grade 1	1 (6.3%)
Grade 2	2 (12.5%)
Grade 3	5 (31.3%)
Grade 4	6 (37.5%)
Grade 5	2 (12.5%)

Note: Grade 1: no improvement; Grade 2: 1%–24% improvement; Grade 3: 25%–49% improvement; Grade 4: 50%–74% improvement; Grade 5: 75%–100% improvement.

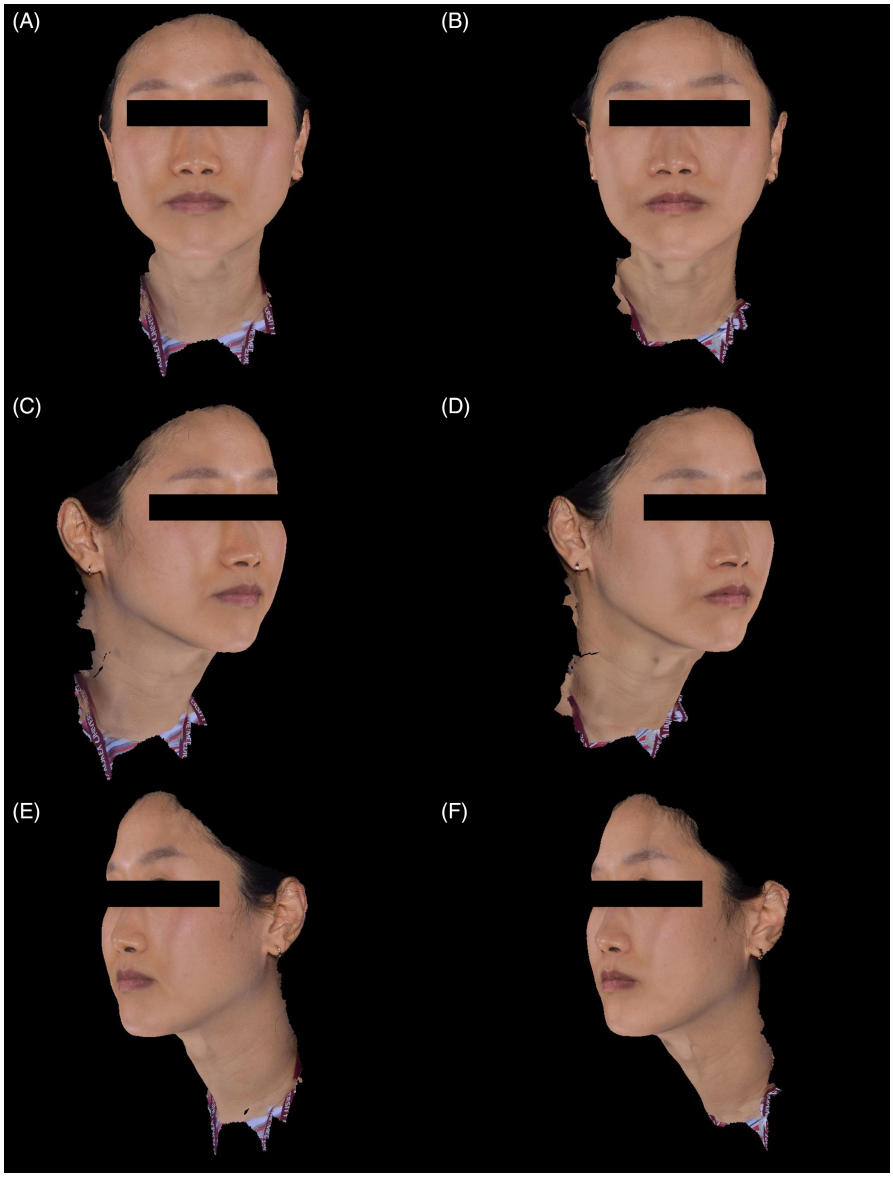

FIGURE 3 3D photographs of a 35-year-old female (A,C,E) before treatment and (B,D,F) at 16 weeks after two treatment sessions. Post-procedure photographs show remarkable improvement of facial erythema in both cheeks (pretreatment score of fine wrinkles: 4, and posttreatment score of fine wrinkles: 4; pretreatment score of skin texture: 6, and posttreatment score of skin texture: 4; pretreatment score of irregular pigmentation: 6, and posttreatment score of irregular pigmentation: 4; pretreatment score of telangiectasia: 6, and posttreatment score of telangiectasia: 3; pretreatment score of facial erythema: 7, and posttreatment score of facial erythema: 4).

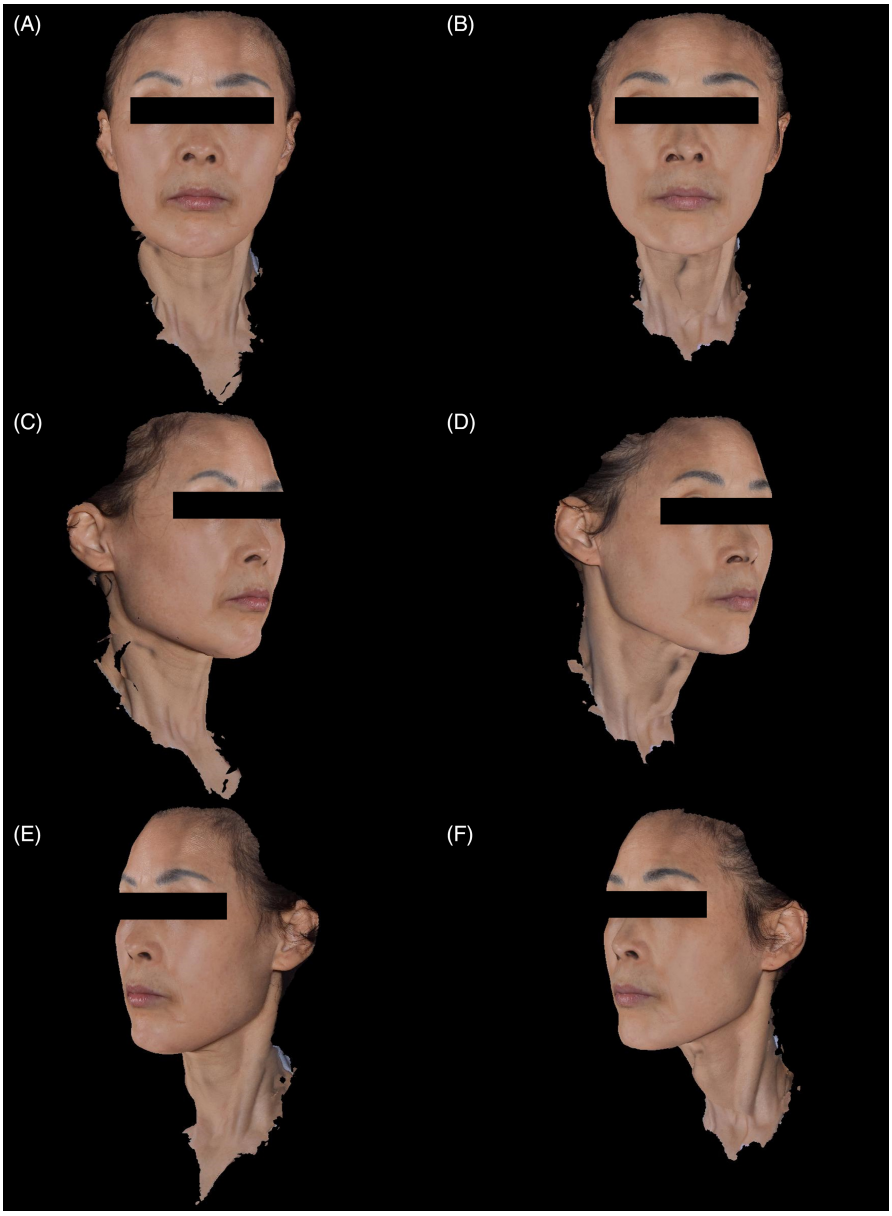

FIGURE 4 3D photographs of a 55-year-old female (A,C,E) before treatment and (B,D,F) at 16 weeks after two treatment sessions. Post-procedure photographs show remarkable improvement in skin texture and irregular pigmentation in the forehead, cheeks, and chin (pretreatment score of fine wrinkles: 7, and posttreatment score of fine wrinkles: 5; pretreatment score of skin texture: 6, posttreatment score of skin texture: 4, pretreatment score of irregular pigmentation: 7; posttreatment of irregular pigmentation: 4; pretreatment score of telangiectasia: 6, and posttreatment score of telangiectasia: 6; pretreatment score of facial erythema: 6, and posttreatment score of facial erythema: 5).

conditions, such as lentigines or melasma, which are associated with photoaging. The alteration of the dermal matrix due to photoaging plays a significant role, and we believe that improving the dermal milieu through PDLLA injection contributed to the amelioration of irregular pigmentation. Additionally, unlike other outcomes, some patients experienced aggravation of facial erythema. This aggravation can be explained by findings of recent animal and cell experiments showing that PDLLA microspheres can induce angiogenesis. The authors highlighted that PDLLA could induce angiogenesis in endothelial cells and lead to a subsequent decrease in ROS of fibroblasts, which can impact skin rejuvenation.[23]

No significant procedure-related adverse events were observed. Some patients experienced aggravation of facial erythema and procedural pain. Similar to the aforementioned, angiogenesis is thought to be related to facial erythema aggravation.[23] Facial erythema could be due to angiogenesis or transient irritation by the procedure.

The two patients received treatment three times because the therapeutic efficacy was not evident during the initial stages of the protocol. Their age, 54 and 55, was not significantly older than the other 14 patients. It could be explained by the fact that PDLLA microspheres tend to decompose slowly and gradually impact skin rejuvenation. However, there was no significant difference in therapeutic effect between these two patients and the rest of the patients, meaning that the skin rejuvenation effect should be tracked longer.

This study has several limitations. First, the number of participants was insufficient to obtain statistical power. We referred to a single-arm study assessing the human tissue response to injectable PLLA for sample size estimation. This study involved 14 patients

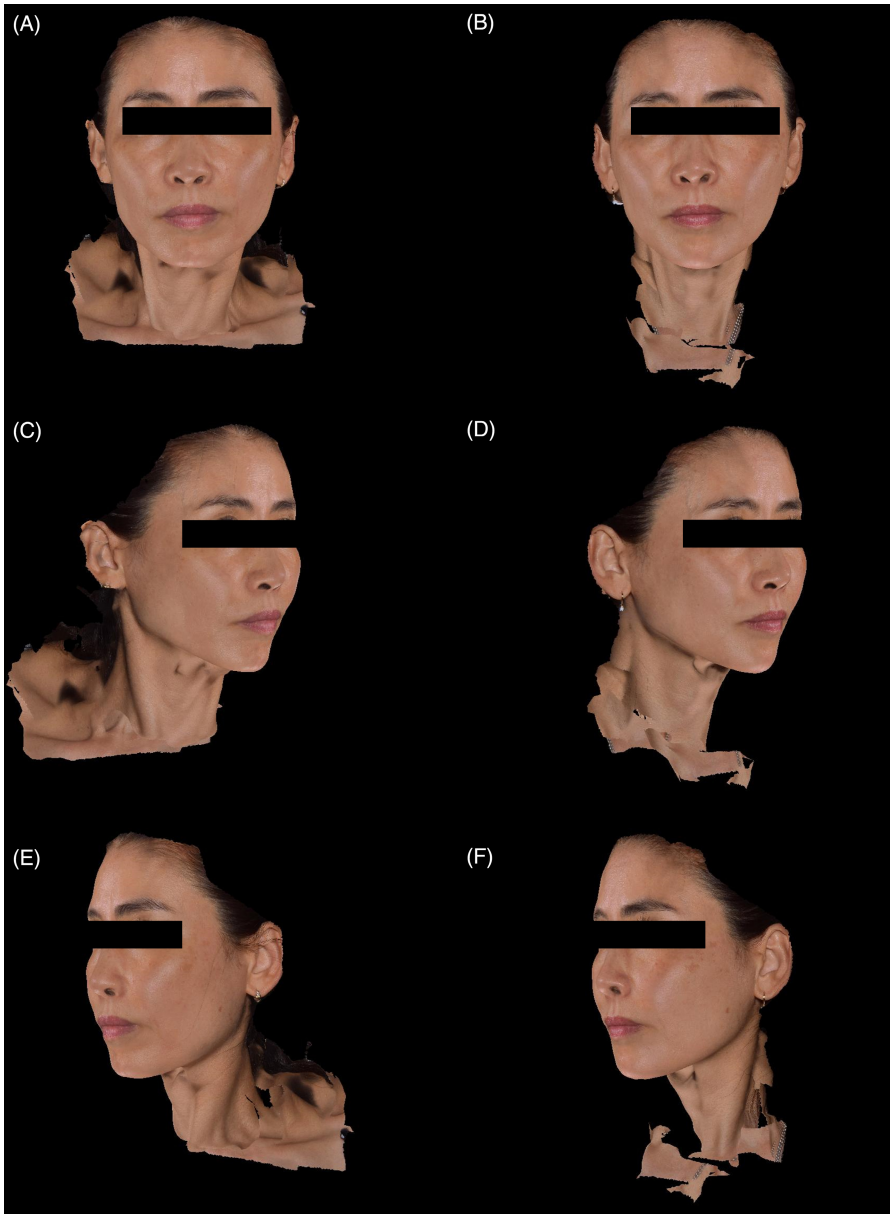

FIGURE 5 3D photographs of a 51-year-old female (A,C,E) before treatment and (B,D,F) at 16 weeks after two treatment sessions. Post-procedure photographs show skin contouring effect, especially in both mandible areas (pretreatment score of fine wrinkles: 6, and posttreatment score of fine wrinkles: 4; pretreatment score of skin texture: 6, and posttreatment score of skin texture: 5; pretreatment score of irregular pigmentation: 7, and posttreatment score of irregular pigmentation: 6; pretreatment score of telangiectasia: 5, and posttreatment score of telangiectasia: 4; pretreatment score of facial erythema: 5, and posttreatment score of facial erythema: 4).

TABLE 4 Adverse events during treatment session visits and follow-up visits.

	Adverse event					
	Aggravation of erythema	Procedural pain	Bruise	Swelling/edema	Blisters/crust	Others
N, (%)	4 (25.0%)	3 (18.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

and demonstrated statistically significant results.[24] However, compared to other studies, the sample size in this study was relatively small.[20,22] Therefore, increasing the sample size in future research would be more beneficial for power analysis. Second, only Koreans participated in the study, making it difficult to generalize findings to the entire population, including FST I, II, V, and VI. Third, there was a partial lack of objectivity in analyzing this study's outcome. Lastly, the relatively brief follow-up period in this study posed challenges in assessing the long-term impact of PDLLA. However, 3D photographs and histologic examination through EVG and MT staining supported this study's findings.

5 | CONCLUSION

According to this preliminary study, injectable dermal PDLLA could significantly rejuvenate skin without causing serious adverse events. Furthermore, after treatment sessions, histopathologic evaluation

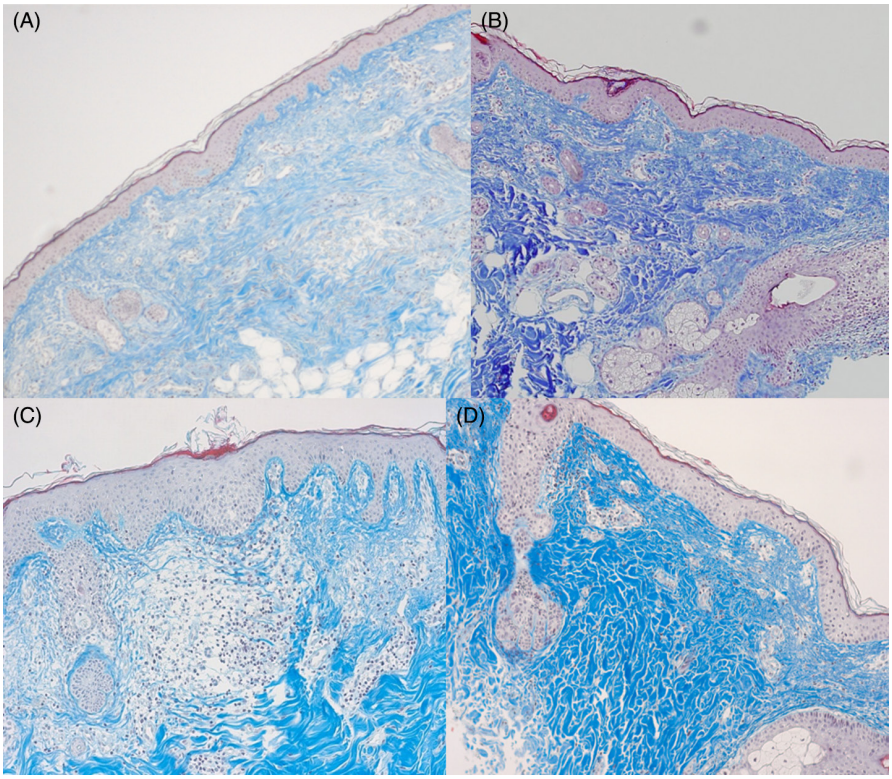

FIGURE 6 Histology with MT staining (X100) of posterior auricular area (A,C) before treatment and (B,D) at 16 weeks after the final treatment session. Post-procedural histologic examination demonstrates increase of collagen fibers within the dermis.

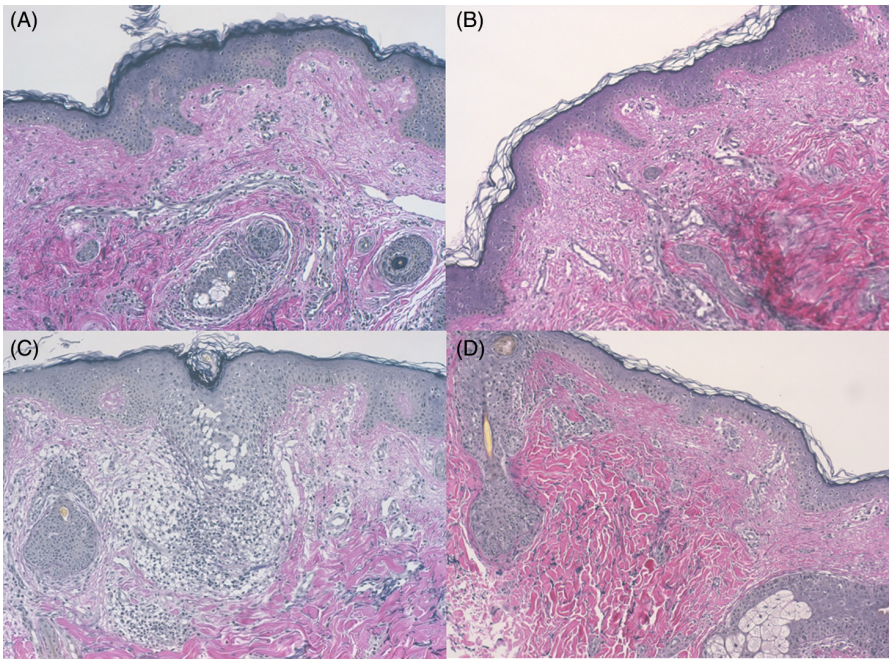

FIGURE 7 Histology with EVG staining (X100) of posterior auricular area (A,C) before treatment and (B,D) at 16 weeks after the final treatment session. Post-procedural histologic examination demonstrates increased and thickened elastic fibers within the dermis.

demonstrated increased collagen and elastic fiber in the dermis (especially the papillary dermis). Although subsequent research is needed, injectable dermal PDLLA could be an effective and safe treatment option for skin rejuvenation in patients with skin aging changes.

AUTHOR CONTRIBUTIONS

Seo SB, Park H, Jo JY, and Ryu HJ performed the research. Seo SB, Jo JY, and Ryu HJ designed the research study. Park H, Jo JY, and Ryu HJ analyzed the data. Seo SB, Jo JY, and Ryu HJ wrote the paper.

ACKNOWLEDGMENTS

This work was supported by VAIM Co., LTD. (Okcheon, Korea). The funder had no role in design of the study; in the collection, analyses, or interpretation of data; or in the decision to publish the results.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to and the appropriate ethical review committee approval has been received. The protocol of this study was approved by the Institutional Review Board (IRB) of Korea University Ansan Hospital (IRB no. 2022AS0008).

REFERENCES

1. Tzellos TG, Klagas I, Vahtsevanos K, et al. Extrinsic ageing in the human skin is associated with alterations in the expression of hyaluronic acid and its metabolizing enzymes. *Exp Dermatol*. 2009;18(12):1028-1035. doi:10.1111/j.1600-0625.2009.00889.x
2. Amano S. Possible involvement of basement membrane damage in skin photoaging. *J Investig Dermatol Symp Proc*. 2009;14(1):2-7. doi:10.1038/jidsymp.2009.5
3. Liebel F, Kaur S, Ruvolo E, Kollias N, Southall MD. Irradiation of skin with visible light induces reactive oxygen species and matrix-degrading enzymes. *J Invest Dermatol*. 2012;132(7):1901-1907. doi:10.1038/jid.2011.476
4. Courderot-Masuyer C, Robin S, Tauzin H, Humbert P. Evaluation of the behaviour of wrinkles fibroblasts and Normal aged fibroblasts in the presence of poly-L-lactic acid. *J Cosmet Dermatol Sci Appl*. 2012;2(1):20-27. doi:10.4236/jcdsa.2012.21006
5. Cabral LRB, Teixeira LN, Gimenez RP, et al. Effect of hyaluronic acid and poly-L-lactic acid dermal fillers on collagen synthesis: an in vitro and in vivo study. *Clin Cosmet Investig Dermatol*. 2020;13:701-710. doi:10.2147/CCID.S266015
6. Sánchez-Carpintero I, Candelas D, Ruiz-Rodríguez R. Dermal fillers: types, indications, and complications. *Actas Dermosifiliogr*. 2010;101:381-393. doi:10.1016/s1578-2190(10)70660-0
7. Kruglikov IL, Wollina U. Soft tissue fillers as non-specific modulators of adipogenesis: change of the paradigm? *Exp Dermatol*. 2015;24:912-915. doi:10.1111/exd.12852
8. Wise JB, Greco T. Injectable treatments for the aging face. *Facial Plast Surg*. 2006;22:140-146. doi:10.1055/s-2006-947720
9. Wu DC, Karnik J, Margarella T, Nguyen VL, Calame A, Goldman MP. Evaluation of the in vivo effects of various laser, light, or ultrasound modalities on human skin treated with a collagen and polymethylmethacrylate microsphere dermal filler product. *Lasers Surg Med*. 2016;48:811-819. doi:10.1002/lsm.22580
10. Kwon TR, Han SW, Yeo IK, et al. Biostimulatory effects of polydioxanone, poly-d,l lactic acid, and polycaprolactone fillers in mouse model. *J Cosmet Dermatol*. 2019;18(4):1002-1008. doi:10.1111/jocd.12950
11. Oh S, Seo SB, Kim G, et al. Poly-D,L-lactic acid filler increases extracellular matrix by modulating macrophages and adipose-derived stem cells in aged animal skin. *Antioxidants*. 2023;12(6):1204. doi:10.3390/antiox12061204
12. Oh S, Lee JH, Kim HM, et al. Poly-L-lactic acid fillers improved dermal collagen synthesis by modulating M2 macrophage polarization in aged animal skin. *Cell*. 2023;12(9):1320. doi:10.3390/cells12091320
13. Lin IJY, Lin CY. Injectable poly-D, L-lactic acid in facial rejuvenation: three case reports. *Cosmetol J*. 2020;4:000120.
14. Lin JY, Lin CY. Nonsurgical lower eyelid rejuvenation using injectable poly-d,l-lactic acid in Asian patients. *J Cosmet Dermatol*. 2022;21(10):4328-4331. doi:10.1111/jocd.15047
15. Roh NK, Kim MJ, Lee YW, Choe YB, Ahn KJ. A split-face study of the effects of a stabilized hyaluronic acid-based gel of non-animal origin for facial skin rejuvenation using a stamp-type multineedle injector: a randomized clinical trial. *Plast Reconstr Surg*. 2016;137(3):809-816. doi:10.1097/01.prs.0000480686.68275.60
16. Youn CS, Hong JY, Park KY, Kim BJ, Nam Kim M. A review of hydrolifting: a new modality for skin rejuvenation. *J Cosmet Laser Ther*. 2018;20(1):28-33. doi:10.1080/14764172.2017.1358459
17. Sito G, Manzoni V, Sommariva R. Vascular complications after facial filler injection: a literature review and meta-analysis. *J Clin Aesthet Dermatol*. 2019;12(6):E65-E72.
18. Heydenrych I, Kapoor KM, De Boulle K, et al. A 10-point plan for avoiding hyaluronic acid dermal filler-related complications during facial aesthetic procedures and algorithms for management. *Clin Cosmet Investig Dermatol*. 2018;11:603-611. doi:10.2147/CCID.S180904
19. Lin CY, Lin JY, Yang DY, et al. Efficacy and safety of poly-D,L-lactic acid microspheres as subdermal fillers in animals. *Plast Aesthet Res*. 2019;6:16. doi:10.20517/2347-9264.2019.23
20. Hyeong JH, Jung JW, Seo SB, et al. Intradermal injection of poly-d,l-lactic acid using microneedle fractional radiofrequency for acne scars: an open-label prospective trial. *Dermatol Surg*. 2022;48(12):1306-1311. doi:10.1097/DSS.0000000000003627
21. Storer M, Euwer R, Calame A, Kourosh AS. Late-onset granuloma formation after poly-l-lactic acid injection. *JAAD Case Rep*. 2016;2(1):54-56. doi:10.1016/j.jdcr.2015.11.017
22. No YA, Seok J, Hyun MY, et al. Long-term (24-month) safety evaluation of poly-DL-lactic acid filler injection for the nasolabial fold: a multicenter, open, randomized, evaluator-blind, Active-controlled design. *Plast Reconstr Surg*. 2015;135(6):1074e-1075e. doi:10.1097/PRS.0000000000001247
23. Oh S, Seo SB, Kim G, Batsukh S, Son KH, Byun K. Poly-D, L-lactic acid stimulates angiogenesis and collagen synthesis in aged animal skin. *Int J Mol Sci*. 2023;24(9):7986. doi:10.3390/ijms24097986
24. Goldberg D, Guana A, Volk A, Daro-Kaftan E. Single-arm study for the characterization of human tissue response to injectable poly-L-lactic acid. *Dermatol Surg*. 2013;39(6):915-922. doi:10.1111/dsu.12164 Epub 2013 Mar 6.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Seo SB, Park H, Jo JY, Ryu HJ. Skin rejuvenation effect of the combined PDLLA and non cross-linked hyaluronic acid: A preliminary study. *J Cosmet Dermatol*. 2024;23:794-802. doi:10.1111/jocd.16085