Facial Skin Rejuvenation Using Poly-DL-Lactic Acid Injected With a Laser-Generated Needle-Free Microjet Injector

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BACKGROUND A laser-induced needle-free microjet injector was developed for rapid, high-speed drug delivery of microliters into the skin.

OBJECTIVE This study evaluated the clinical rejuvenation effect of repeated dermal injections of the collagen simulator poly-DL-lactic acid (PDLA) using a laser-induced needle-free microjet injector.

METHODS Five PDLA injection sessions using a laser-induced needle-free microjet injector were conducted in patients concerned about aging skin. Facial uplifting, darkness, redness, roughness, pore size, subjective satisfaction, and side effects were evaluated before each session and 4 weeks after treatment completion. Histological evaluation was also performed with immunohistochemical staining of collagen and elastic fibers.

RESULTS The clinical results of 27 female patients were evaluated. The treatment resulted in a noticeable skin surface uplifting (0.711 ± 0.42 mm) and significant improvements in darkness ($p = .013$), redness ($p = .009$), and roughness ($p = .036$), with no significant difference in the pore size ($p = .770$). Patients were reported being satisfied with the overall therapeutic effects, despite mild and tolerable adverse effects. Histological findings revealed growth and thickening of collagen and elastic fibers, with marked increase in collagen I and III levels.

CONCLUSION Repeated dermal injections of PDLA using a laser-induced microjet injector offer excellent drug delivery, achieving high efficacy in skin rejuvenation, patient satisfaction, and safety.

As life expectancy increases, the desire to maintain a beautiful appearance for extended periods intensifies. With the increasing interest in antiaging, various procedures have been developed, including laser skin resurfacing, intense pulse light therapy, chemical peels, dermabrasion, microneedling, dermal fillers, and botulinum toxin therapy. Among these interventions, poly-DL-lactic acid (PDLA) mesotherapy, a type of polylactic acid (PLA) filler, stands out as a remarkable option.

Poly-DL-lactic acid is an US Food and Drug Administration–approved filler medication with proven long-term (24 months) safety and efficacy and used for various applications such as scar treatment and skin rejuvenation.[1] Manually administering PDLA with conventional syringes poses challenges in delivering minute, even amounts of the drug across the entire thin dermis. Consequently, drug delivery devices, such as mesoguns or microneedle systems, employing multiple small needles to uniformly administer a predetermined quantity of medication at a consistent depth, have been developed for various drug injections.[2–4] However, the use of needles for drug injections induces pain and requires a recovery period from injection-related wounds and irritation. Patients increasingly prefer noninvasive or minimally invasive treatments.

The recently developed laser-induced needle-free jet injector (NFJI), which converts laser light energy into kinetic pressure for drug delivery, is gaining attention owing to its ability to administer minute drug quantities evenly into the dermis without the use of needles.[5] Although previous studies at this institution have explored the effects of intradermal injection of PDLA through microneedle radiofrequency, reports on the clinical outcomes and side effects of PDLA therapy administered through the laser-induced NFJI are lacking.[4] Therefore, the authors investigated the efficacy and safety of PDLA injections using the laser-induced NFJI.

Materials and Methods

Patients and Ethical Approval

This study was approved by the Institutional Review Board of Hallym University Sacred Hospital, Korea (IRB Number: HALLYM 2023-04-007), and the study protocol was approved by the Ethics Committee of Hallym University Medical Center. Recruited participants were individuals visiting the Dermatology Clinic at Hallym University Sacred Heart Hospital between May 2023 and November 2023. Inclusion criteria encompassed individuals aged ≥20 years

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The authors have indicated no significant interest with commercial supporters.

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Dermatol Surg 2024;00:1–7
http://dx.doi.org/10.1097/DSS.0000000000004195

who consented to clinical trial participation. A single dermatologist performed all procedures. Exclusion criteria comprised individuals who had undergone cosmetic procedures, including laser therapy, peeling, botulinum toxin injection, or fillers within the past 6 months; pregnant women; and those with treatment site infections, facial dermatitis, known PDLA allergy, or a keloid history. The study protocol adhered to the ethical guidelines outlined in the Declaration of Helsinki, and informed consent was obtained from all participating patients.

Treatment Device

The laser-induced NFJI (Mirajet; JSK Biomed, Daejeon, Korea) operates as a transdermal drug delivery system, injecting drugs without needles, by converting intense light energy from an Er:YAG laser into kinetic pressure (Figure 1). When the laser focuses on the water in the cylinder, it induces cavitation, leading to the generation of powerful pressure that pushes the elastic membrane outward. This sequence produces a microjet of the drug, allowing for dermal drug delivery without the use of needles.

Poly-DL-Lactic Acid Dermal Filler

The collagen stimulator used in this study is the PDLA filler (Juvelook, VAIM, Korea), a formulation combining 42.5 mg of PDLA with 7.5 mg of hyaluronic acid.

Protocol

Patients underwent 5 PDLA injection sessions using the PDLA dermal filler at 3- to 4-week intervals. All treatments were performed by a single dermatologist identically following the outlined protocol. A local anesthetic cream ([eutectic mixture of local anesthetics] EMLA, lidocaine 2.5%, and prilocaine 2.5%) was applied before the procedure to alleviate pain.

Two hours before treatment, the authors diluted 16 mg of PDLA in 3 cc of normal saline by vortexing. Laser settings included a 200 μm-sized nozzle, operating at 30 Hz frequency, with the Er:YAG laser power set between 70 and 90 mJ. Each treatment session employed a painting technique used in laser toning, delivering the injection across the entire facial area in 2 to 3 passes until dispensing a total of 3 cc of the diluted PDLA solution. This process involved approximately 15,000 pulses per session, with each pulse delivering 0.2 μL of the solution into the skin at

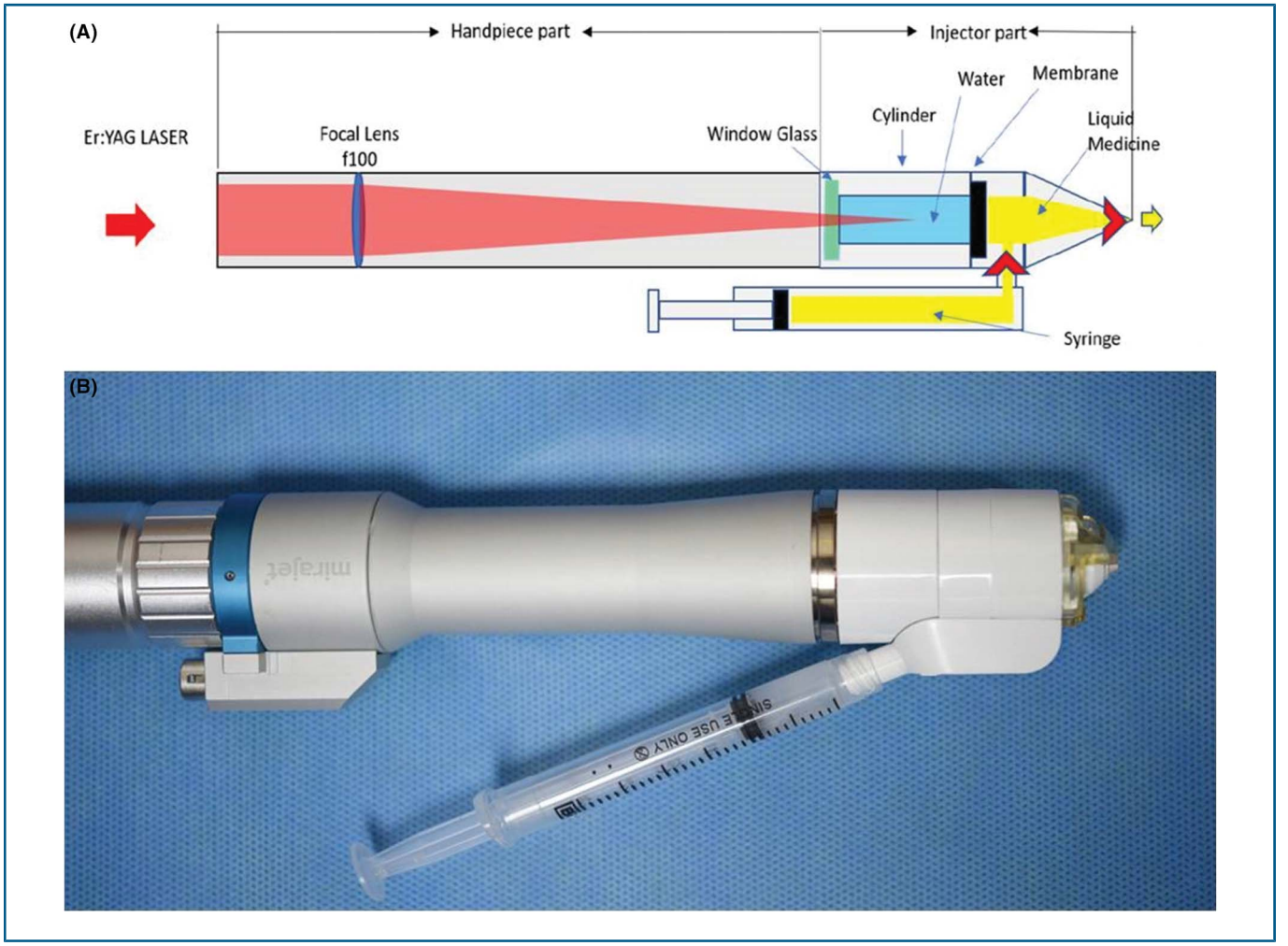

Figure 1. (A) The mechanism of laser-induced needle-free microjet injector. A concentrated beam of high-energy laser is observed, generating a powerful burst of force. (B) The nozzle of "Mirajet" for drug delivery. The nozzle connects with the needle-free microjet injector.

jet speed. No other treatments were done to the face until the completion of all sessions.

Clinical Assessment

Photographs of the patients were taken at baseline, immediately after each treatment session, and 4 weeks after the final session using a Nikon D40 camera (Nikon, Tokyo, Japan) for comprehensive assessment. Patients also underwent A-one Lite imaging (Bomtec, Seoul, Korea) for a detailed analysis of specific clinical changes such as vessels and pigmentation and 3D imaging (LifeViz Mini; Quantificare, Sophia Antipolis, France). All the photographs were taken by the same photographer, and 2 dermatologists exempted from previous treatments assessed the clinical images after treatment.

Skin darkness, redness, roughness, and pore size were evaluated on a 5-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe).[6] Overall improvement was assessed using the Global Aesthetic Improvement Scale (GAIS; 1 = exceptional improvement; 2 = very improved; 3 = improved; 4 = unaltered; and 5 = worsened). In the before-and-after evaluation process of the study, the raters were successfully blinded to the chronological sequence of the photographs.

Furthermore, the dermatologists evaluated the facial uplifting effects by analyzing vector changes using the 3D image program. This program automatically compared before-and-after photographs captured with a 3D camera, evaluating the extent of lifting in millimeters for each area of the entire facial region and illustrating it with yellow arrows. To conduct an objective comparative analysis, the face was categorized into 6 groups: left and right upper cheeks (periorbital area), midcheek, and lower cheek (perioral area). A representative yellow arrow, termed the "landmark vector," was chosen for each area. The sizes (in mm) of these vectors were aggregated, and the authors referred to this averaged vector change as "3D pixel movement." Size variations were quantified as positive values when the vector pointed against gravity and negative values when it pointed towards gravity. Side effects such as erythema, bruising, swelling, itching, burning sensation, altered sensation, and postinflammatory hyperpigmentation were also evaluated immediately after each treatment.

Subjective Assessment of the Patients

One month after completion of the 5-session treatment, patient satisfaction was assessed using a 5-point scale questionnaire (0 = no improvement; 1 = 1%–25% improvement; 2 = 26%–50% improvement; 3 = 51%–75% improvement; and 4 = 76%–100% improvement). Pain was evaluated immediately after treatment using the visual analog scale (VAS), ranging from 0 (no pain) to 10 (worst and excruciating pain), and postprocedural downtime was investigated.

Histological Assessment

Two consenting patients underwent 2 mm skin biopsies in the postauricular area adjacent to the treated skin before and 4 weeks after completion of the 5-session treatment. Tissue samples were collected and evaluated for dermal changes by hematoxylin and eosin (H&E), Masson's trichrome, and Verhoeff–van Gieson staining. Collagen I and III staining (Novus Bio., Centennial, CO) was also performed for a detailed examination of the dermal collagen composition. The authors used ImageJ software (NIH, Bethesda, MD) for quantitative analysis of histological changes within the dermis. This software enabled a comprehensive assessment of staining levels for structural components such as collagen, collagen I, collagen III, and elastin fibers, which exhibited distinct staining characteristics. By customizing this analysis with ImageJ, the authors effectively measured area fractions of stained collagen and elastin fibers.

Statistical Analysis

A paired *t*-test was conducted to assess changes before and after treatment. SPSS for Windows (version 26.0) was used for statistical analysis, and $p < .05$ was considered statistically significant.

Results

Patient Characteristics

All 27 patients who successfully completed the 5 sessions were exclusively Korean females with an average age of 48.56 ± 10.90 years. The Fitzpatrick skin types were classified in 13 individuals as type III and 14 as type IV (Table 1).

Clinical Assessment

Table 2 provides a comprehensive objective assessment of skin rejuvenation. Skin darkness, redness, and roughness demonstrated statistically significant positive responses, as presented in Figures 2 and 3 (2.500 vs 2.042, $p = .013$; 2.083 vs 1.542, $p = .009$; and 2.333 vs 1.958, $p = .036$, respectively). Although the pore size improved after treatment, the difference was not statistically significant (2.208 vs 2.166; $p = .770$). 3D pixel movement for face lifting revealed a prominent positive response, with no movement in 4 individuals, 0 to 1 mm in 14 individuals, 1 to 2 mm in 6 individuals, and 2 mm or more in 3 individuals (Figure 4). The average observed movement was 0.711 ± 0.42 mm. With an average score of 2.208 ± 1.190, the GAIS indicates a "very improved" overall treatment effect. Some patients had tolerable side effects, with 3 individuals

TABLE 1. Demographics of Patients

	No. of Subjects
Age, yr	48.56 ± 10.90
Sex	
Female	27 (100%)
Fitzpatrick skin type	
III	13 (48.15%)
IV	14 (51.85%)

TABLE 2. Objective Clinical Assessment of Change in Darkness, Redness, Roughness, and Pore Size Before Treatment and 4 Weeks After the Fourth Treatment Session and GAIS, 3D Pixel Movement, and Subjective 5-Point Scale Results After Treatment

	Pretreatment	Post-treatment	*p*
Darkness	2.500 ± 0.764	2.042 ± 0.934	.013*
Redness	2.083 ± 0.640	1.542 ± 0.644	.009**
Roughness	2.333 ± 0.745	1.958 ± 0.789	.036*
Pore size	2.208 ± 0.706	2.166 ± 0.687	.770
3D pixel movement (mm)	—	0.711 ± 0.42	
GAIS	—	2.208 ± 1.190	
Subjective 5-point scale	—	2.542 ± 1.079	

Values are presented as number or mean ± SD.
Statistical analysis of the difference between 2 groups is expressed as *$p < .05$ and **$p < .01$.
GAIS, Global Aesthetic Improvement Scale.

exhibiting mild erythema during the procedure, which resolved spontaneously within an average recovery downtime of 1.933 ± 0.346 days. In addition, 6 individuals experienced mild folliculitis, but all cases improved within 5 days of topical antibiotic application. No other side effects were reported, such as bruising, swelling, itching, burning sensation, altered sensation, or postinflammatory hyperpigmentation.

Subjective Assessment of the Patients

The 5-point scale that assessed subjective patient responses yielded an average score of 2.542 ± 1.079 (Table 2); particularly, on average, the patients perceived 26% to 50% improvement after 5 sessions. In addition, the VAS scores for pain after each session averaged around 1.118 ± 0.185, indicating minimal discomfort.

Histopathological Findings

Skin biopsies were conducted on 2 patients through H&E staining, Verhoeff–van Gieson staining, and Masson's trichrome staining before and after treatment with PDLA injected with a needleless injector. After treatment, H&E staining revealed an overall increase and thickening of dermal collagen bundles (Figure 5A,B). Verhoeff–van Gieson and Masson's trichrome staining also revealed increased thickness and density of collagen and elastin fibers in the papillary dermis and mid-dermis after treatment, with no evidence of granuloma formation (Figure 5C–F). After treatment, collagen I and III levels increased pronouncedly (Figure 5G,H). Quantitative analysis using ImageJ for collagen, collagen I, collagen III, and elastic fibers in the dermis demonstrated increased proportions of all these elements after treatment, as outlined in Table 3.

Discussion

Based on clinical and histological findings, the study demonstrated that PDLA injections using a laser-induced microjet injector totaling 5 sessions are an effective treatment option for skin rejuvenation, minimizing pain and other adverse effects.

In skin rejuvenation mesotherapy, a broad spectrum of agents is used, including vitamins, enzymes, hormones, and plant extracts, as well as specialized compounds such as hyaluronic acid, exosomes, polynucleotides, and PLA. Polylactic acid, an eco-friendly biodegradable polymer, promotes collagen synthesis and increases skin volume when injected into the skin.[7–9] Poly-DL-lactic acid, a type of PLA with an average particle size of 30 μm and a round foam structure, facilitates smooth injection into the human skin, while minimizing side effects such as palpable nodules. In animal study, it was demonstrated that PDLA modulates macrophages to promote the proliferation of adipose-derived stem cells, ultimately leading to increased collagen synthesis.[10] Several clinical studies have validated the capacity of PDLA for collagen synthesis in scar and rejuvenation treatments, using various injection methods including manual needle injection, microneedle fractional radiofrequency devices, mesotherapy injectors, and NFJIs.[4,11–13] In a recent study, 3 individuals undergoing needle-free jet injections of PDLA for atrophic acne scars exhibited noticeable skin rejuvenation effects.[11] In addition, a split-face study revealed enhanced skin hydration and elasticity following a single session of PDLA injection using

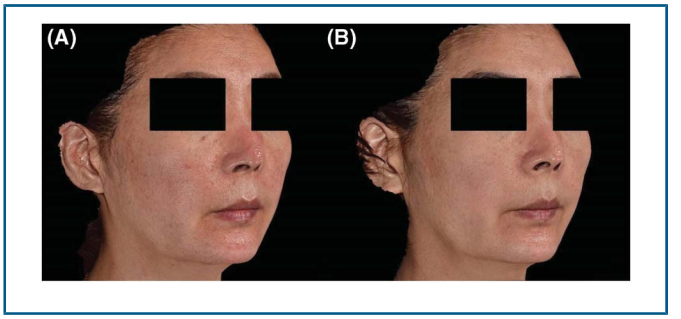

Figure 2. Prominent improvement in the overall redness and darkness is observed in 3D images (A) before and (B) after treatment.

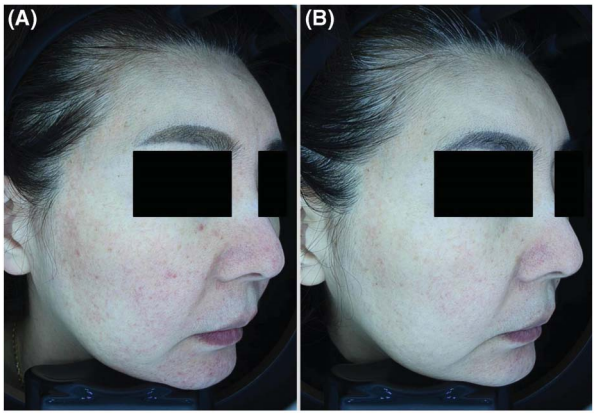

Figure 3. Clinical photographs in a polarizing light view before (A) and after (B) treatment. Reduced vascular and pigment components are observed after treatment.

the NFJI; however, no significant alterations were observed in texture, wrinkles, and pores.[12] On the contrary, this study confirmed significant improvements in darkness, redness, and roughness after 5 sessions of PDLA injection using the NFJI, along with an observable face uplifting effect. The results suggest that undergoing multiple sessions, rather than just 1, could potentially amplify the rejuvenating effects of PDLA injections through the NFJI. Further studies are necessary to confirm this hypothesis and to determine the optimal number of sessions.

The effectiveness of this treatment method in rejuvenation implies that PDLA is efficiently injected through the NFJI. In a cadaver study using the laser-induced NFJI for PDLA injection, the histological findings demonstrated precise drug delivery into the papillary dermal layer (depth of 300 μm).[5] Another study using a laser system for the NFJI reported that the delivery efficiency of various viscosities, ranging from 1 to 58 MDa, into artificial skin was 78% to 95% when injected at 13–27 μL/pulse.[14] Considering the injection of 140-kDa polymer PDLA in this treatment at 0.2 μL/pulse, the authors infer that the treatment also exhibits high delivery efficiency after observing the histological changes in the papillary dermis and mid-dermis after treatment. During PDLA injection through the NFJI, optimal jet power settings should be established. Excessive jet power may lead to side effects such as pain, bleeding, and skin damage. The jet power varies depending on the nozzle diameter and jet velocity, influencing jet penetration, dispersion, and quantitative delivery of the jet.[15] Cofactors such as the mechanical properties of the skin, jet volume, and standoff distance also contribute to drug delivery. As the standoff distance increases, the material ejected from the nozzle tip accelerates even further before reaching the skin, ultimately resulting in a faster injection speed into the dermis. Lifting the device tip off the skin during the procedure may allow for easier control of the device's handpiece and thus shorten the procedure time but could increase jet velocity, causing more pain, bleeding, and skin damage. Therefore, the authors conducted the procedure with the device tip nearly touching the skin. Using this technique, they were able to achieve therapeutic effects while avoiding adverse effects such as swelling or holes.

The injection of PDLA using the NFJI synergistically enhanced the PDLA effectiveness. Some authors have proposed that microtrauma from drug injection through the NFJI induces a healing response, potentially extending the dermal changes caused by PDLA.[16] In addition, NFJI-assisted PDLA injections offer advantages concerning side effects, pain, downtime, and procedure time, thereby enhancing patient compliance. A study on porcine tissue revealed that an infinitesimal injection volume of the microjet minimizes tissue destruction, consequently reducing the side effects.[14] This procedure also demonstrated only tolerable side effects, and the microjet facilitated the even injection of minute amounts of PDLA, preventing side effects such as granulation from excessive PDLA injection. In another study by the team, the procedure of injecting PDLA using a microneedle fractional radiofrequency device for acne scars resulted in an average VAS score of 3.9 ± 1.3 and the recovery downtime for erythema after the

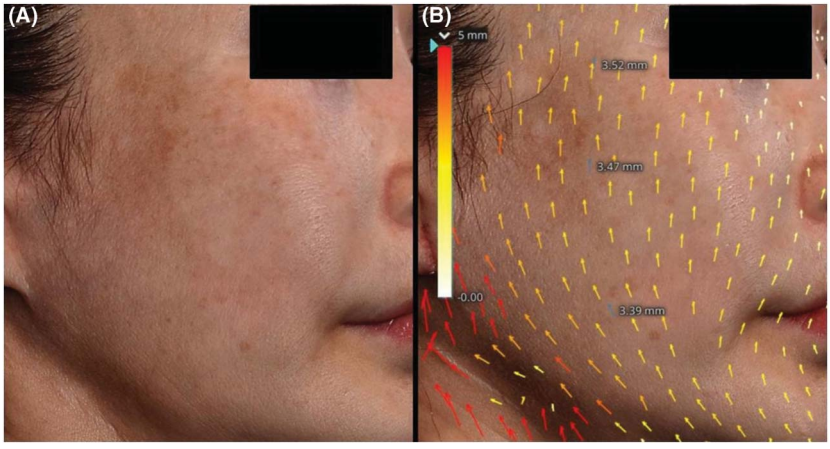

Figure 4. Clinical photographs before (A) and after (B) treatment. The upward 3D pixel movement shows the uplifted face after treatment completion (yellow arrows).

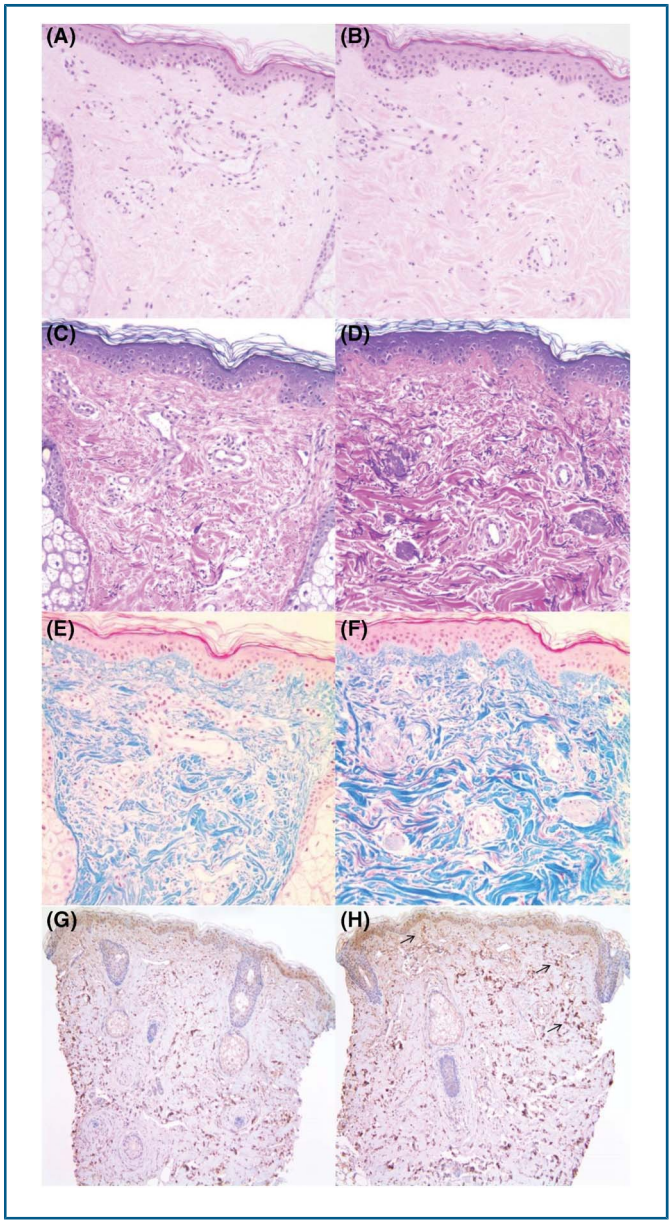

Figure 5. Hematoxylin and eosin staining (A and B) shows increased and thickened collagen bundles in the upper dermis and mid-dermis after treatment. Pretreatment (A) and post-treatment (B) (×200). Staining for Verhoeff–van Gieson staining (C and D) and Masson's trichrome staining (E and F) show increased and thickened collagen bundles and elastin fibers after treatment. Pretreatment (C and E) and post-treatment (D and F) (×200). Immunohistochemical staining for collagen III (G and H). Black arrows indicate the areas where collagen III has increased. Pretreatment (G) and post-treatment (H) (×100).

procedure was 2.62 ± 1.03 days,[4] contrary to the VAS score of 1.118 ± 0.185, indicating less pain, and the decreased downtime of 1.933 ± 0.346 days in this study. In a split-face study that confirmed the clinical effects of PDLA injection using the laser-induced NFJI, the reported VAS score for pain was 5.39 ± 2.01.[12] Unlike the administration of 3 cc across the entire face, the increased pain reported in the split-face study was attributed to the 2-cc injection on half the face, utilizing a slightly higher output energy of 100 mJ. Moreover, the procedure in this study, averaging approximately 5 minutes to administer a single ampul of PDLA, is generally time efficient.[12,14] In summary, the benefits of reduced side effects, diminished pain, shorter recovery time, and faster procedure durations considerably alleviate patient concerns about receiving the treatment. Consequently, the repeated dermal injection of PDLA through the laser-induced NFJI emerges as an optimal treatment choice for skin rejuvenation, benefiting from the synergistic impact and enhanced patient compliance.

TABLE 3. Area Fraction (%) of Dermal Collagen and Elastic Fiber Area Measured Before Initial Treatment and 4 Weeks After Treatment Completion

	Pretreatment (%)	Post-treatment (%)	Ratio
Collagen	50.23	59.95	1.19
Collagen I	39.12	43.27	1.11
Collagen III	38.92	49.89	1.28
Elastic fiber	37.17	48.11	1.29

This study had several limitations. First, given the limited number of biopsies, additional investigation with more extensive biopsy sample sizes is required. Second, all enrolled participants were Korean females with skin types III and IV, precluding the evaluation of males and individuals of other races. Third, the analysis of the study outcomes displayed a partial lack of objectivity. At last, this study did not observe outcomes beyond 1 year. However, clinico-histological evaluations were conducted after the theoretical period for collagen boosting with PDLA, thereby attributing importance to the findings.

Conclusion

A laser-induced microjet injector with PDLA is a suitable treatment option for facial rejuvenation in patients with skin types III and IV. This drug delivery system allows precise control over the depth and quantity of drug injection, enabling rapid administration without needle usage. This results in minimal pain and side effects and reduced downtime, ultimately achieving satisfactory therapeutic outcomes. It can be an optimal treatment option for patients with sensitive skin, needle phobia, or pain concerns.

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