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CLINICAL REPORT

Needleless laser injector versus needle injection for skin enhancement and rejuvenation effect of dermal filler

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Abstract

Background and Objectives: A needleless laser-induced microjet injector is a novel transdermal drug delivery system that can rapidly inject a very small and precise drug dose into the skin with minimal pain and downtime. In this study, we aimed to compare the laser-induced microjet injection versus needle injection of polylactic acid/hyaluronic acid filler for skin enhancement and rejuvenation.

Patients and Methods: A 24-week prospective, single-center, assessor-blinded, randomized, split-face study was conducted. The enrolled patients underwent one treatment session of dermal filler injection using a laser-induced microjet injector on one half of the face or a traditional needle injection on the other half of the face. Evaluation was conducted at baseline before treatment and at 4, 12, and 24 weeks after treatment.

Results: A single treatment of filler injection with a laser-induced microjet injector resulted in similar improvements in skin hydration and elasticity as a single treatment of filler injection by using manual needle injection, with reduced pain, side effects, and decreased treatment time.

Conclusions: Laser-induced microjet injector enabled not only the application of a controlled dose and filler depth but also even distribution, improved clinical efficacy, reduced pain and side effects, and sufficient time for clinicians to perform treatment.

KEYWORDS

dermal filler, hyaluronic acid, needleless injector, needleless laser injector, polylactic acid, skin rejuvenation

INTRODUCTION

Recently, there has been increasing interest in the use of fillers as mesotherapy to restore healthy, youthful, and moisturized skin beyond its traditional use for the correction of deep wrinkles or for the replacement of volume.[1] Traditional filler mesotherapy is performed manually by using a syringe with a needle and by using the multipuncture/micropapule technique, which allows small amounts of filler to be injected into the superficial dermis.[2,3] It is the simplest and most economical method, but it has drawbacks such as pain during procedures, needle fear/phobia, possibility of irregular and inaccurate injections, and long treatment time.[4]

To overcome these disadvantages, mesogun multineedle injectors or needleless jet injectors that use compressed springs or gas (pneumatic pressure) as an energy source have been used.[1] Although these methods allow for more stable and accurate injections than manual injection techniques, there are still limitations owing to the restricted adjustability of the amount of input energy during the injection of the target material. Therefore, they still have drawbacks such as

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limited range of jet volume that can be injected, low injection velocity, inaccurate injection depth, significant pain due to tissue dissection, and long downtime (Online Supporting Information: Table S1).[1,5–7]

There has been growing interest on needleless injectors that use laser energy.[8,9] Mirajet (JSK Biomed) was the first laser-induced microjet injector to acquire Conformité Européenne certification for medical devices in the European Union, and this device uses an Er:YAG laser that generates vapor bubbles to generate pressure energy.[4] It is composed of two chambers: an upper chamber filled with water and a lower chamber filled with injection material. When the laser is focused and blasted in the upper chamber, the pressure generated by the explosion pushes the membrane downward, thus leading to the microjet injection of the drug (Figure 1). The main advantage of this laser-induced microjet injector is the precise control over energy deposition, thus allowing for the accurate injection of a very small volume (0.0003 mL) into a precise depth (superficial to deep dermis). Furthermore, injections can be performed at a rapid rate of 40 shots per second with minimal pain.[5,10]

One study used Mirajet to inject polylactic acid (PLA)/hyaluronic acid (HA) composite filler into five Korean cadavers and observed that PLA/HA filler substances were localized precisely and uniformly at the same level of the papillary dermis.[4] However, no clinical study has been conducted on living humans for the evaluation of the skin rejuvenating effect after PLA/HA injection by using this laser-induced microjet injector. In the current study, we conducted a single-center, randomized, double-blind, split-face clinical study to compare the laser-induced microjet injection versus needle injection of PLA/HA filler to achieve skin enhancement and rejuvenating effects.

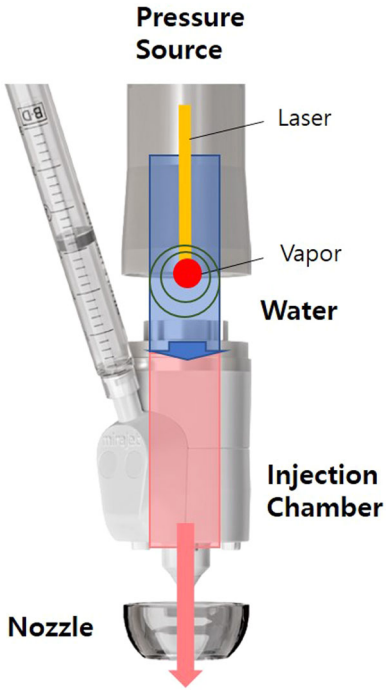

FIGURE 1 Laser-induced microjet injector consisting of a pressure source, injection chamber, and nozzle. A microjet is generated by a focused laser beam that expands the vapor bubbles, and the injection substance is injected into the skin by the pressure produced by the vapor bubbles.

MATERIALS AND METHODS

Study design and patient enrollment

A 24-week prospective, single-center, assessor-blinded, randomized, split-face study was conducted to compare the clinical efficacy and safety of needless laser injectors versus needle injections for the antiaging effect of dermal fillers (ClinicalTrials.gov Identifier: NCT05685667). This study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (IRB No. B-2105-682-003) and was performed in conformance with the CONSORT 2010 guidelines.

Adults aged 25−60 years old who wanted to enhance or rejuvenate their skin were recruited. The exclusion criteria included subjects with history of skin rejuvenation treatment (including filler, botulinum toxin, lasers, chemical peeling, and topical retinoid) within 6 month before the start of the study, subjects who plans to undergo skin rejuvenation treatment during the study, who is pregnant or breastfeeding, who is allergic to PLA or HA (Online Supporting Information: Table S2). The enrolled patients underwent one treatment session of dermal filler injection using a laser-induced microjet injector on one half of the face or a traditional needle injection on the other half of the face. Evaluation was conducted at baseline before treatment and at 4, 12, and 24 weeks after treatment. The design of this randomized clinical trial is shown in Online Supporting Information: Figure 1.

Randomization and blinding

A random number table was used for randomization. Half of each patient's face was randomized consecutively to either the laser-induced microjet injection group (experimental group) or the needle injection group (control group) at the time of enrollment. The left/right assignment was sealed in a nontransparent envelope. The treating dermatologist (J. W. S.) was not blinded or involved in the evaluation.

Preparation of PLA/HA composite dermal filler

A PLA/HA filler (Juve Look; Vaim Medical) was used. One vial containing 42.5 mg of PLA and 7.5 mg of HA

was diluted with 8 cc of normal saline and vortexed for 2 h before use.

Treatment protocol

All patients underwent a single treatment session. Before treatment, a topical anesthetic cream was applied on the entire face of each subject. After gently cleansing the face, the patients wore protective eyeshields, and patients were injected with a PLA/HA composite dermal filler by using a laser-induced microjet injector on one half of the face and a traditional method of needle injection on the other half of the face.

The laser-induced microjet injector was set with a nozzle size of 250 μm, frequency of 20 Hz, and output energy of 80 mJ for treatment in the periorbital area and 100 mJ for treatment in other areas. The laser setting was based on the previous unpublished data that evaluated histology of living human skin after PLA/HA injection using laser-induced microjet injector (Online Supporting Information: Figure 2). To summarize briefly, PLA/HA injection with laser setting with nozzle size of 200 μm and the output energy of 80 mJ on the temple area resulted in PLA/HA filler deposition in the upper dermis. The injection was performed with two to three passes across the face until a total of 2 cc of diluted PLA/HA solution was completely injected. In the traditional method of needle injection, intradermal injection using the multi-puncture/micropapule technique using 1 cc syringe with 31 G needle was used. A series of injections (0.5−1 cm apart) was performed on one half of the face so that a total of 2 cc of diluted PLA/HA solution was injected.

Clinical outcome assessment

Evaluation was conducted at baseline before treatment and at 4, 12, and 24 weeks after treatment. The primary outcomes were on-site biophysical measurements, including skin hydration and elasticity. The biophysical parameters were measured by a blinded experienced dermatologist (B. R. K.). Skin hydration was measured using a Corneometer® CM 825 (Courage & Khazak), and skin elasticity was measured using a Cutometer® MPA 580 (Courage & Khazaka) at 2 cm below the point where the horizontal line starting from the nasal ala and the vertical line starting from the midpupil met. Among the various parameters of the Cutometer® MPA 580, R2 (gross elasticity) and R8 (ability of the skin to return to the normal state) were measured. The patients were instructed not to apply any cosmetics and not to wash their faces within 2h before the measurements. All measurements were performed by the same investigator in a room with constant temperature (23°C) and humidity (45%).

The secondary outcomes were the objective measurements of skin surface topography analyzed by 3D photogrammetry and the patient's subjective evaluation of satisfaction with the enhancement of the skin, pain during treatment, and degree of recovery after treatment. To objectively measure the parameters related to skin aging, such as skin texture, wrinkles, and pores, the 3D images of each patient's lateral canthus area were obtained using an Antera 3D® camera (Miravex Limited) at every visit. The images were then analyzed using dedicated software with a small filter suitable for the analysis of fine lines and pores. Objective measurements for skin aging included texture-related parameters (Ra, Rq, and Rt), wrinkle-related parameters (indentation index and maximum depth), and pore-related parameters (area and volume). The detailed explanations of each parameter are provided in Online Supporting Information: Table S3.

Patient satisfaction scores for antiaging effects were evaluated from 1 (extremely dissatisfied) to 7 (extremely satisfied) at 4, 12, and 24 weeks after treatment and were compared with the scores before treatment. Pain during treatment was measured using a visual analog scale (VAS) from 0 (none) to 10 (worst). The degree of recovery on the third day after treatment was divided into erythema, bruises, and crust (marks at the injection site), and each was measured by VAS. Adverse events related to the procedure were assessed by one investigator (B. R. K.), and patients were required to report any adverse events during the treatment and follow-up periods.

Sample size and statistical analysis

A sample size of 33 patients (33 pairs) was sufficient to detect a clinically important difference of 5.5 in skin hydration (arbitrary unit) between paired groups, assuming a standard deviation (SD) of 10 by using a paired *t*-test with 80% power and 5% level of significance.[11] Our initial estimate of the sample size assumed a dropout rate of 15%.

Categorical variables are presented as frequencies and proportions, whereas continuous variables are presented as means and SDs. Each measurement at the follow-up visit was compared with the baseline value by using the Wilcoxon signed-rank test. An independent samples *t*-test was used to compare the average values of the experimental group versus control group at each follow-up visit. The results are expressed as mean ± SD, and $p < 0.05$ was considered statistically significant. IBM SPSS version 20 (IBM Corp.) was used to analyze all data.

RESULTS

A total of 57 patients were screened for eligibility. Twenty-four patients were excluded because they refused to participate ($n = 3$), did not meet the inclusion criteria

($n = 5$), or did not meet the exclusion criteria ($n = 16$). In total, 33 patients met the eligibility criteria and were randomized, among which 32 completed the study. One patient dropped out during the follow-up period because of difficulties in following the visit schedule.

Baseline characteristics and treatment time

Table 1 presents the patients' basic characteristics. The mean patient age was 38.44 ± 5.39 years (range: 27−50 years), and 87.5% of the study population was female. Most patients (96.9%) had Fitzpatrick skin type III or IV, whereas 3.1% of patients had type II skin.

Changes in biophysical measurements: Skin hydration and elasticity

Compared with the baseline, the average skin hydration significantly increased in the experimental group at Weeks 4, 12, and 24. In the control group, skin hydration also increased after treatment compared with the baseline, but the changes were not statistically significant (Figure 2A). In both groups, skin hydration increased over Weeks 4 and 12, but slowly decreased at Week 24. However, the values at Week 24 were still higher than those at baseline in both groups.

Among the values related to the measured skin elasticity, the R2 value significantly increased in the experimental group at Weeks 4, 12, and 24 compared with the baseline. In the control group, the R2 value also increased over time, but the changes were statistically significant only at Weeks 12 and 24 (Figure 2B). Similarly, the R8 value significantly increased in the experimental group at Weeks 4, 12, and 24 compared with that at baseline. In the control group, the R8 value also increased over time, but the changes were statistically significant only at Weeks 12 and 24 (Figure 2C). Therefore, although skin elasticity increased in both experimental and control groups, the changes were faster in the experimental group.

TABLE 1 Patients' baseline demographic characteristics.

	Total ($n = 32$)
Fitzpatrick skin type	
II, *n* (%)	1 (3.13)
III, *n* (%)	18 (56.25)
IV, *n* (%)	13 (40.63)
Sex	
Male, *n* (%)	4 (12.5)
Female, *n* (%)	28 (87.5)
Age	
Mean ± SD	38.44 ± 5.39

Changes in skin surface topography: Texture, wrinkle, and pore

In the experimental group, the values of texture-related parameters decreased (indicating improvement in skin roughness) at Weeks 4 and 12 compared with the baseline but slowly recovered at Week 24. By contrast, in the control group, texture-related parameters increased at Weeks 4 and 12 (indicating worsening skin roughness) compared with the baseline but slowly recovered at Week 24. However, there was no statistically significant difference between the two groups (Figure 3A).

Similarly, among the wrinkle-related parameters, the indentation index slightly decreased at Weeks 4 and 12 in the experimental group compared with the baseline but slowly recovered at Week 24. On the other hand, in the control group, the indentation index increased at Weeks 4 and 12 compared with the baseline but slowly decreased at Week 24. In addition, the maximum depth increased in both the experimental and control groups at Week 4 compared with the baseline but slowly decreased from Week 12. However, there was no statistically significant difference between the two groups at each follow-up visit (Figure 3B).

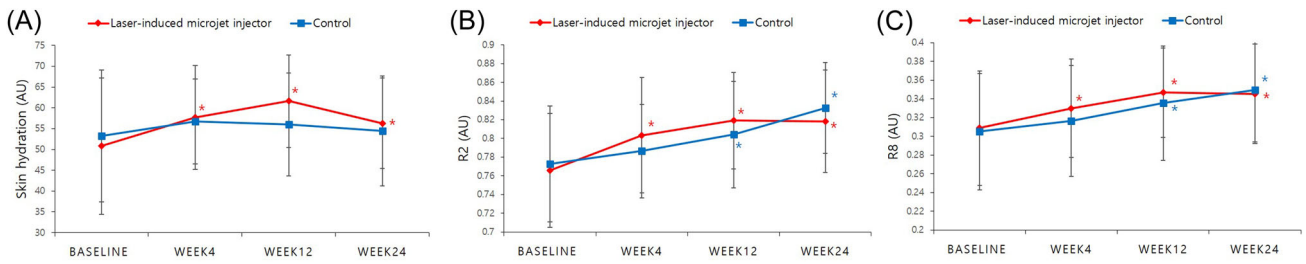

FIGURE 2 Changes in biophysical measurements. Changes in skin hydration (A), skin elasticity R2 (B), and skin elasticity R8 (C) values after dermal filler injection using a laser-induced microjet or needle injection (control). *$p < 0.05$. AU, arbitrary unit.

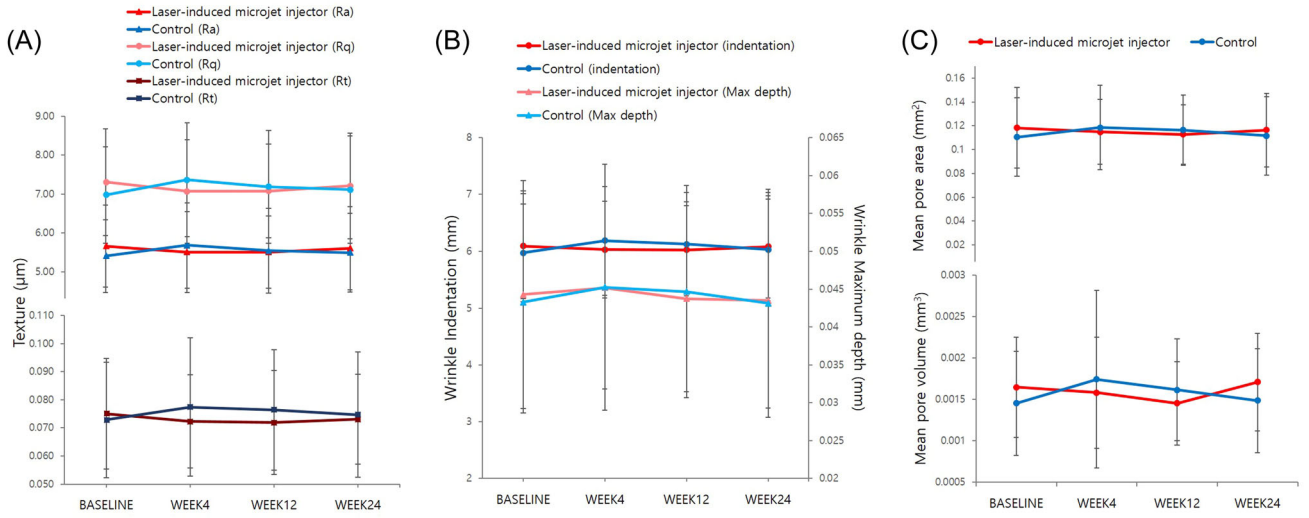

FIGURE 3 Changes in objective measurements in skin aging. Changes in texture-related parameters (Ra, Rq, Rt) (A), wrinkle-related parameters (indentation index and maximum depth) (B), and pore-related parameters (mean pore area and mean pore volume) (C) after dermal filler injection using a needleless laser injector or needle injection. $*p < 0.05$.

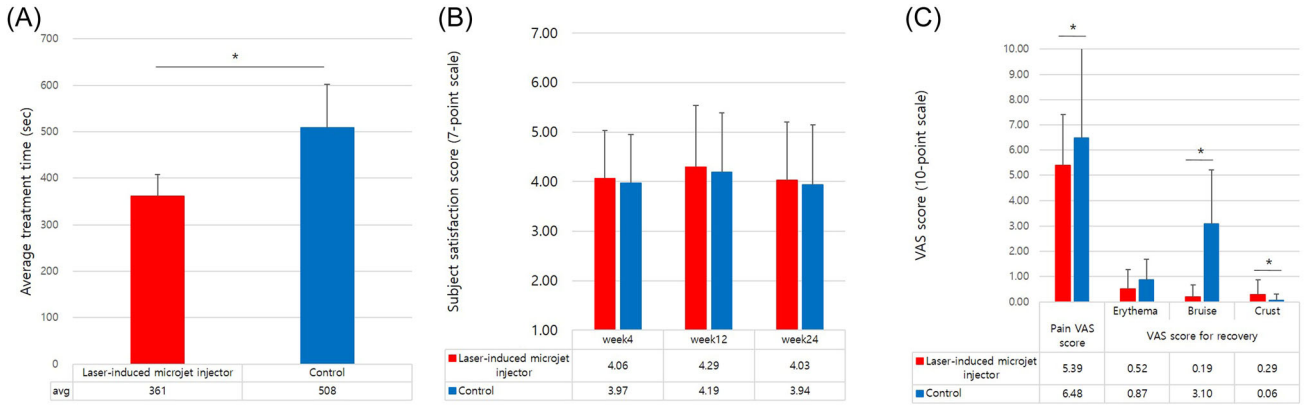

FIGURE 4 Average treatment time (A), subject satisfaction score (B), and treatment pain and recovery related visual analog scale (VAS) scores (C) after dermal filler injection using a needleless laser injector or needle injection. $*p < 0.05$.

Among pore-related parameters, the mean pore area and mean pore volume decreased at Weeks 4 and 12 in the experimental group but recovered at Week 24. In the control group, the mean pore area and mean pore volume increased at Weeks 4 and 12 but slowly decreased at Week 24. However, there was no statistically significant difference between the two groups at each follow-up visit (Figure 3C).

Treatment time and scores for patient's satisfaction, pain, and degree of recovery

The treatment time was significantly shorter with laser-induced microjet injection than with manual injection (361 ± 47.17 vs. 508 ± 93.40 s, $p < 0.001$) (Figure 4A). Furthermore, according to the patients' subjective satisfaction evaluation, patient satisfaction was the greatest at Week 12 in both groups. Although the differences were not statistically significant, the overall satisfaction scores were greater in the experimental group than in the control group (Figure 4B).

The average VAS score for pain during treatment was significantly lower in the experimental group than in the control group (5.39 ± 2.01 vs. 6.48 ± 6.50, $p = 0.009$). The average VAS score for erythema after treatment was also lower in the experimental group than in the control group but the difference was not statistically significant (0.52 ± 0.77 vs. 0.87 ± 0.81, $p = 0.058$). The VAS score for bruising at the injection site was also significantly lower in the experimental group than in the control group (0.19 ± 0.48 vs. 3.10 ± 2.12, $p < 0.001$). By contrast, the VAS score for crust after treatment was significantly higher in the experimental group than in the control

FIGURE 5 Clinical photographs on the third day after treatment. There were fewer bruises and erythematous wheals at the injection sites in the laser-induced microjet injection group than in the control group.

group (0.29 ± 0.59 vs. 0.06 ± 0.25, $p = 0.035$) (Figure 4C). Figure 5 shows the clinical photographs of two representative cases comparing the degree of recovery after treatment.

Safety

All patients tolerated the treatment well. One case of treatment-related adverse events (delayed immune reaction to filler) occurred in the control group but spontaneously resolved within 5 days without treatment.

DISCUSSION

In this randomized, intraindividually controlled study, the results indicated that the laser-induced microjet injector is a safe and favorable device that can be used for mesotherapy for skin enhancement and rejuvenation. A single treatment of PLA/HA filler injection using a laser-induced microjet injector resulted in similar improvements in skin hydration and elasticity as an injection using manual needle injection but with fewer side effects, shorter treatment time, and shorter downtime.

The biological mechanism of the intradermal injection of PLA/HA fillers for skin enhancement and rejuvenation is well known.[12–14] As the main component of the extracellular matrix, HA draws water into the matrix, thus creating volume, increasing skin turgor, lubricating tissue, improving skin elasticity, and alleviating skin surface roughness.[14–17] PLA is a biocompatible, biodegradable, immunologically inert synthetic polymer that stimulates collagen by inducing an inflammatory reaction that results in neocollagenesis.[18–20] After PLA injection, collagen production starts within 6−8 weeks, and type 1 collagen continues to form up to 9−12 months after treatment.[21,22]

In both the laser-induced microjet injection and control (needle injection) groups, skin hydration and skin elasticity parameters increased after treatment. Notably, skin hydration significantly increased in the laser-induced microjet injection group at 4, 12, and 24 weeks. By contrast, in the control group, the changes were not statistically significant. Similarly, the skin elasticity parameters significantly increased from Week 4 in the laser-induced microjet injection group, whereas the changes were significant from Week 12 in the control group. Therefore, we can infer that the skin hydration and rejuvenating effects were greater and faster when PLA/HA injection was performed using a laser-induced microjet injector. From these results, we can presume that although the primary source of the antiaging effect of PLA/HA injection would be the biological effects of the PLA/HA filler itself, the effect of filler injection can be maximized using different methods of filler delivery into the skin. By using a laser-induced microjet injector, minute doses of filler can be injected into the skin densely at an even distribution and at a constant penetration depth compared with manual injection. Furthermore, the injection can be performed at a constant quality regardless of the clinician's skill, requires less time and energy for the clinician, and results in less pain and downtime for patients. These advantages allow for a more pronounced and stable skin enhancement and antiaging effect of the filler injection while minimizing the associated side effects.

Several interesting findings were noted in the results of the objective measurements analyzed using the Antera 3D® camera. Immediately after treatment, texture-related and pore-related parameters were improved in the laser-induced microjet injection group but worsened in the needle injection group. These results reflect the epidermal damage that occurs during needle injection compared with during laser-induced microjet injection. This was also shown in a previous study using cadavers, where the punctures from the laser injections were not visible on the surface of the skin.[4] Furthermore, although the texture- and wrinkle-related parameters were improved in the laser-induced microjet injection group, the changes were not statistically significant. This may be because treatment was performed only once in the current study. After a single treatment session, maximum

improvement in skin rejuvenation was observed at Week 12 and was slowly reduced afterward, although a moderate effect was maintained until 24 weeks. Therefore, to maximize the antiaging effect of PLA/HA filler injection using a laser-induced microjet injector, it would be beneficial to repeat the treatment several times at intervals of 3 months or less. To confirm this, further studies that evaluate the effect of repeated treatment with variable amounts of PLA/HA injection would be beneficial.

The common side effects associated with dermal filler injections include pain during treatment, erythema, bruising, and crust (marks at the injection site) after treatment. Our results showed that injection with a laser-induced microjet injector significantly decreased pain, erythema, and bruising. As shown in Figure 5, 3 days after the treatment, bruise and erythematous wheals at the injection sites were pronounced at the manual injection site (control), whereas no epidermal changes were observed at the laser-induced microjet injection site. On the other hand, crust formation occurred more frequently when using a laser-induced microjet injector. This result may be attributed to the greater number of valid injections (complete injection of dermal filler at the targeted depth) with laser-induced microjet injectors because such devices allow injections to be performed more densely and constantly. Furthermore, the fine crusts were spontaneously removed without leaving any marks or postinflammatory hyperpigmentation after 3−4 days. From this, we can presume that there was no major vessel damage and thus no inflammation due to vessel damage which can result in postinflammatory hyperpigmentation.

Nodule formation is another frequently reported side effect of dermal filler injection, which requires special attention, particularly during filler mesotherapy.[23–26] The risk of this complication can be minimized by using a laser-induced microjet injector, which enables the injection of a precise amount of filler into a precise depth. In the current study, nodule formation did not occur in either group possibly because manual filler injection was performed by a very skilled clinician with abundant clinical experience. However, nodule formation can easily occur when an unskilled clinician performs the procedure or when performing the procedure in more anatomically vulnerable areas; in these cases, a laser-induced microjet injector would be advantageous. Finally, the treatment time was significantly shorter when a laser-induced microjet injector was used. Therefore, this novel injector device allows for an optimal and time-saving procedure that can maximize skin enhancement and rejuvenation effects and minimize the risk of dermal filler injections. The cost of this device is reasonable (US$ 70,000 for a laser body, US$ 150 for a disposable nozzle) and thus considering the above-mentioned advantages of the use of this device, dermal filler injection using a laser-induced microjet injector can be a competitive treatment method to be used in the esthetic treatment market.

This study has several limitations. Although this study was designed to be a split-face study to minimize the effects of other variables, a long-term follow-up clinical study using a larger sample size is necessary to establish standard protocols for the use of novel injectors. Furthermore, although multiple biophysical parameters were evaluated in this study, future studies that includes clinical evaluation by blinded physician are needed to support clinical significance of this treatment. Also, given that this study focused on Korean subjects, further studies with larger populations and subjects with different skin types and thicknesses are needed to generalize the results. Last but not least, although the previous study using cadavers and unpublished previous data provided histological evidence that the laser-induced microjet injector delivered HA/PLA at superficial dermis, further studies with larger sample size that evaluate histological sections of living human skin using different laser setting or with various injection materials are needed to better support the results of our study.

In conclusion, the use of a specialized laser-based needleless injector enabled not only the application of a controlled dose and depth of the filler but also even distribution, improved clinical efficacy, reduced pain and side effects, and sufficient time for clinicians to perform treatment. Therefore, laser-induced microjet injectors may be a promising new option for dermal filler injection for skin enhancement and rejuvenation and may be useful for pain sensitive or needle-phobic patients.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

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

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