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Investigating the Mechanisms of Intradermal Injection for Easier "Skin Booster" Treatment: A Fluid Mechanics Approach to Determine Optimal Delivery Method

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Background: The use of "skin boosters" for rejuvenating aged skin is widely used. However, the accurate injection of the skin booster into the dermal layer remains a challenge due to the density of the dermis. The purpose of this study was to investigate the optimal mechanical variables of delivery that enabled correct targeting of the product to the dermis for optimal results.

Methods: We investigated the impact of mechanical variables (syringe diameter, needle diameter and length, and viscosity of the skin booster) on the force required for intradermal injection in porcine skin. The correlation between these variables and the injection force was examined as well.

Results: The results show that smaller syringe diameters, larger needle diameters, shorter needle lengths, and lower viscosity of the skin boosters reduce the injection force needed for intradermal injections.

Conclusions: During the administration of skin booster injections, clinicians should take into account optimal conditions that facilitate intradermal injections, thus maximizing rejuvenating outcomes. Furthermore, manufacturers of skin boosters should formulate the products with decreased viscosity and provide the product in conjunction with appropriate needles and syringes, designed to optimize ease of injection. *(Plast Reconstr Surg Glob Open 2024; 12:e5723; doi: 10.1097/GOX.0000000000005723; Published online 8 April 2024.)*

INTRODUCTION

The growing interest in facial rejuvenation is evident in the expanding antiaging treatment industry, with the global market reaching US $60.42 billion in 2021 and projected to hit US $119.6 billion by 2030.[1] Soft tissue filler injections, the second most common cosmetic procedure, stand out for their simplicity and immediate results.[2] Facial aging impacts all face layers, requiring comprehensive treatment.

Rejuvenating layers above the skeleton involves interventions like radiofrequency, ultrasound, botulinum toxin, fillers, and "skin boosters."[3] Coined by Restylane (Q-Med AB, Uppsala, Sweden) in 2015, the term encompasses ingredients such as hyaluronic acid, polydeoxyribonucleotide, oligonucleotide and amino acids, enhancing skin hydration, and texture.[4]

Skin boosters, injected directly into the skin, surpass topical products in delivering active ingredients to the dermis. Precision is crucial to prevent wastage or unintended subcutaneous injection, given the dermal layer's higher density. Despite intradermal injection devices, many physicians prefer manual injection.[5] This study explores mechanical parameters for effective intradermal injection during manual procedures, initiating a series quantifying fluid mechanisms in various injection protocols.

METHODS

The experiments were conducted using porcine skin obtained from the abdominal region of pork at the Korea Institute of Machinery & Materials in Daegu, Republic of Korea. These experiments were carried out in strict

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compliance with the institute's laboratory practice guidelines. The porcine skin used in the study was sourced from commercially available refrigerated pork cuts, which were purchased from a local butcher. These cuts encompassed a range of thickness, extending from the skin to the muscle. Given the ready availability of porcine skin, it was unnecessary to involve live animals in our research. No institutional review board approval was necessary for this experiment because it did not involve human participants or live animals.

Preliminary Experiment

A preliminary study was conducted to investigate the differences in injection force between intradermal and subcutaneous injections in porcine skin. Specimens were obtained from the pork belly region, where the skin and fat layers were clearly distinguished. The specimens were cut into 5 cm × 5 cm pieces, and the force required for intradermal injections and subcutaneous injections were measured and compared using commonly used hyaluronic acid filler.

The placement of the needle tip was confirmed in the dermal and subcutaneous layers by examining the cross-sectional structure of the porcine skin. The injection force was measured using a force gauge (ZTA-100N, IMADA Co., Ltd, Aichi, Japan), whereas a constant flow rate was maintained using a syringe pump (NE-1600, New Era Pump System, Inc, N.Y.; Fig. 1). The flow rate was set to 0.3 mL per minute to resemble the flow rate used by experienced clinicians during injection procedures. The authors aimed to simulate a real-life clinical environment as closely as possible in the conduct of this study. The filler used in the study was a widely used hyaluronic acid filler (QT fill fine, S.THEPHARM Co., Seoul, Republic of Korea), which is commonly used for augmenting soft tissue and also as a low viscoelasticity skin booster. The differences in injection force between intradermal and subcutaneous injections were investigated (Fig. 2).

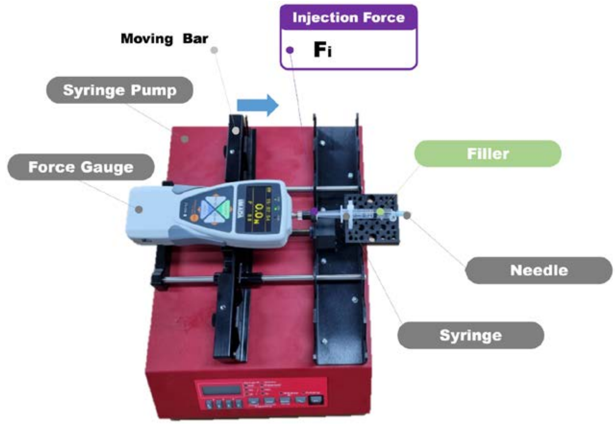

Fig. 1. The injection force was measured using a force gauge (ZTA-100N, IMADA Co., Ltd, Aichi, Japan), whereas a constant flow rate was maintained using a syringe pump (NE-1600, New Era Pump System, Inc, N.Y.). The force at which the filler started to eject from the needle tip was measured, and the peak pressure value recorded during the injection process was defined as the injection force.

> **Takeaways**
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> **Question:** When using skin injectables such as skin boosters, how do you target the intradermal layer more easily?
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> **Findings:** The results show that smaller syringe diameters, larger needle diameters, shorter needle lengths, and lower viscosity of the skin boosters reduce the injection force needed for intradermal injections.
>
> **Meaning:** Clinicians should take into account optimal conditions that facilitate intradermal injections, thus maximizing rejuvenating outcomes. Manufacturers of skin boosters should formulate the products with decreased viscosity and provide the product in conjunction with appropriate needles and syringes, designed to optimize ease of injection.

Main Experiment

The effect of four mechanical variables on the injection force was studied. The variables considered were viscoelasticity of the product, diameter of the syringe, diameter of the needle, and length of the needle.

The effect of viscoelasticity was investigated by diluting the hyaluronic acid filler (QT fill fine, S.THEPHARM, Seoul, Republic of Korea) with normal saline (Microgiene Co., Ltd, Gyeonggi-do, Republic of Korea). Three concentrations of the filler were prepared, including an undiluted solution and two diluted solutions with a solvent (5:1 and 1:1 hyaluronic acid filler to solvent) for a total of three concentrations (100%, 83%, and 50%). Homogeneous mixing was achieved using an ultrasonic mixing device (Bransonic 3800, Emerson Electric Co., Mo.), and the samples were left to equilibrate at 30°C for 24 hours (Fig. 3).

The injection force was measured using a 5 mL syringe with a diameter of 11.6 mm (Feel Ject, Feel Tech Bio Co., Ltd, Gyeonggi-do, Republic of Korea) and needles of 30G 4 mm, 33G 4 mm, and 34G 4 mm (30G 4 mm Sung Sim Medical, Daegu, Republic of Korea; 33G 4 mm and 34G 4 mm Feel Tech Bio Chungnam, Republic of Korea). The syringe pump was connected to a force gauge, and injection was initiated at a constant flow rate of 0.3 mL per minute. The force at which the filler started to eject from the needle tip was measured, and the peak pressure value recorded during the injection process was defined as the injection force (Fig. 4).

The effect of syringe inner diameter (size) on injection force was evaluated by using undiluted hyaluronic acid filler stock solution and a 1:1 solution of the filler diluted with physiological saline, which were each placed in 1 mL, 3 mL, and 5 mL syringes (Feel Ject, Feel Tech Bio Co., Ltd, Gyeonggi-do, Republic of Korea). Intradermal injections were performed using a 33G 4 mm needle while maintaining a constant flow rate of 0.3 mL per minute. Injection force was measured during the injections (Fig. 5).

The effect of needle length on injection force was evaluated by connecting a 30G 4-mm and a 30G one-half inch needle (Jung Rin Medical Industrial Co., Ltd. Chungbuk, Republic of Korea) to the syringe pump and measuring the injection force while maintaining a flow rate of 0.3 mL per minute (Fig. 6).

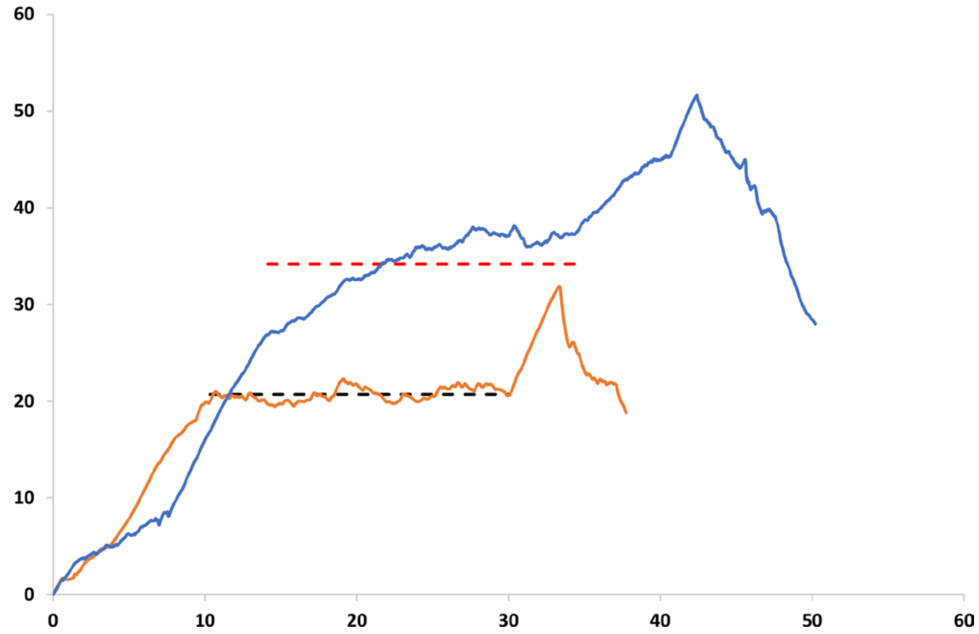

Fig. 2. A preliminary study was conducted to evaluate the differences in the force required for intradermal and subcutaneous injections in porcine skin. The results showed that the average force required for intradermal injection was 34.2 N, whereas the average force for subcutaneous injection was 20.7 N. This indicates a significant difference in the force required, with intradermal injection necessitating a higher force compared with subcutaneous injection (*P* < 0.001, *t* test assuming homogeneity of variance, 95% CI).

Fig. 3. The effect of viscoelasticity was investigated by diluting the hyaluronic acid filler with normal saline. Three concentrations of the filler were prepared, including an undiluted solution and two diluted solutions with a solvent (5:1 and 1:1 hyaluronic acid filler to solvent) for a total of three concentrations (100%, 83%, and 50%). Homogeneous mixing was achieved using an ultrasonic mixing device (Bransonic 3800, Emerson Electric Co., Mo.), and the samples were left to equilibrate at 30°C for 24 hours.

For all experimental conditions, five independent trials were performed, and the average value was calculated by removing the maximum and minimum values and taking the mean of the remaining three data points.

The theoretical basis for excluding the maximum and minimum values when calculating the mean in an experiment is a statistical method aimed at mitigating the impact of outliers and obtaining a more accurate representation of the central tendency. According to the central limit theorem, the distribution of the sample mean approximates a normal distribution when the sample size is sufficiently large. This implies that even in the presence of outliers, the mean calculated from the entire dataset can be more stably estimated.

However, given that the sample size (N) in this study is not large, it was anticipated that the influence of outliers could be significant. Therefore, in the research design phase, we decided to exclude the maximum and minimum values when calculating the mean to minimize the potential impact of outliers.

STATISTICAL ANALYSIS

We collected experimental results, computed the mean and SD, and visually represented the data graphically. Statistical analysis was conducted through the utilization of the *t* test, with data analysis performed using the Excel (Microsoft Corporation, Redmond, Wash.) program.

RESULTS

Preliminary Experiment

As illustrated in Figure 2, the results indicate that intradermal injection necessitates notably higher force compared with subcutaneous injection. The average force required for intradermal injection was 34.2 N, whereas the average force for subcutaneous injection was 20.7 N. This indicates a substantial difference in the force required, with intradermal injection necessitating a higher force

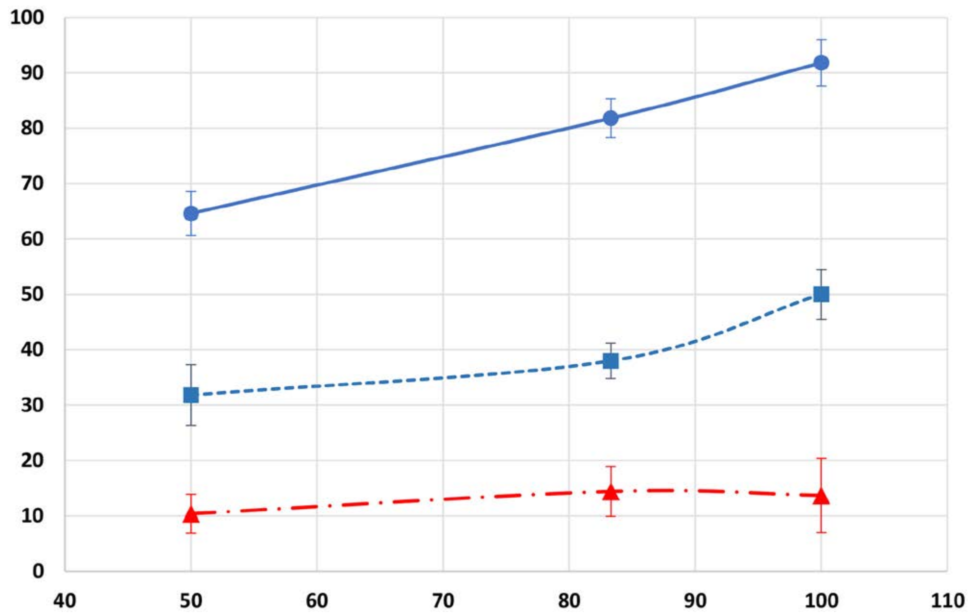

Fig. 4. The influence of viscoelasticity of the skin booster and the diameter of the syringe on the injection force was investigated. The injection force was determined for three concentrations (100%, 83%, and 50%) with three needles of equal length but varying diameters (30G, 33G, and 34G), using a consistent syringe size. The results indicate that an increase in filler concentration leads to an increase in the injection force required. Furthermore, a negative correlation is apparent between needle diameter and injection force. A two-tailed *t* test, assuming homogeneity of variance, was conducted to compare the force. The analysis revealed a statistically significant difference between both 34G needles and 33G needles and 33G needles and 30G needles, with *P* values of 0.006 and 0.0039 at a 95% CI, respectively.

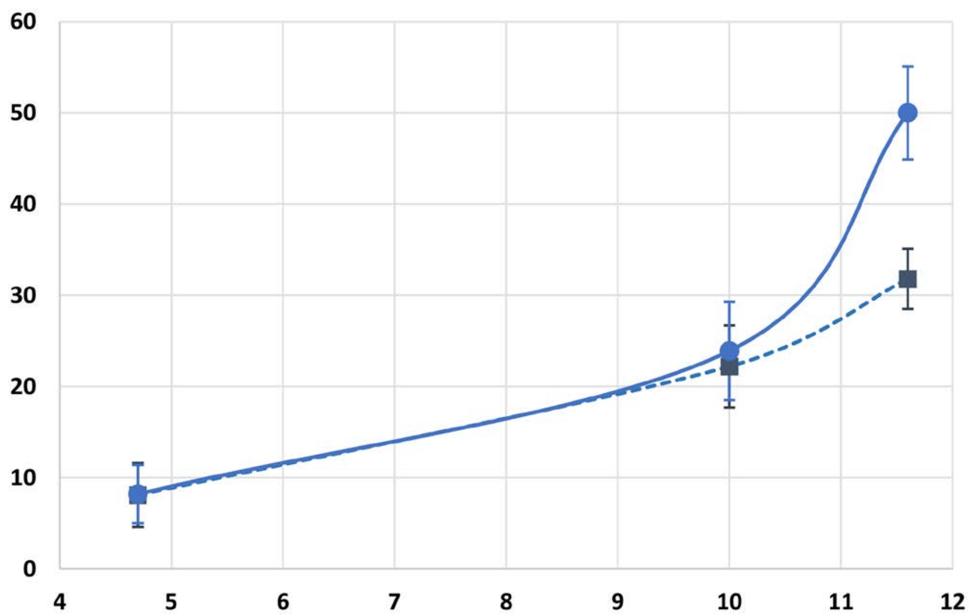

Fig. 5. The effect of the inner diameter of the syringe on injection force was evaluated by using undiluted hyaluronic acid filler stock solution and a 1:1 solution of the filler diluted with physiological saline, which were each administered using 1-mL, 3-mL, and 5-mL syringes. The results demonstrate a positive correlation between the diameter of the syringe and the injection force required to deliver the filler material. Notably, the data indicate that the growth in force conforms to an exponential trend rather than to a linear one, as the syringe diameter expands ($P < 0.001$, based on a *t* test assuming equal variances, with a 95% CI).

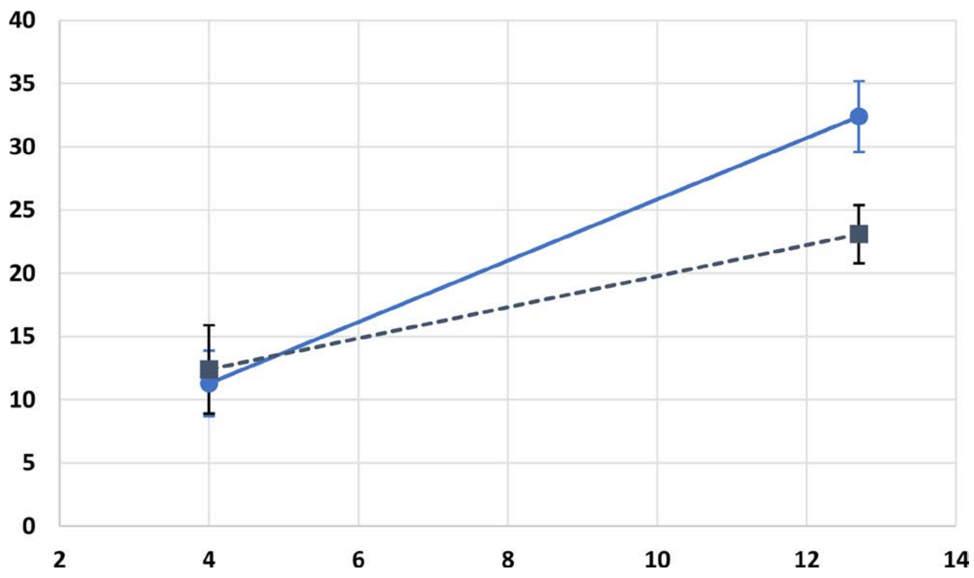

Fig. 6. The influence of needle length on injection force was evaluated using a needle of 4 mm and one-half inch (12.7 mm) in length with a constant diameter of 30G. The results indicate that as the length of the needle increased, the force required for intradermal injection correspondingly increased ($P < 0.001$, based on a *t* test assuming equal variances, with a 95% CI).

compared with subcutaneous injection [$P < 0.001$, *t* test assuming homogeneity of variance, 95% confidence interval (CI)].

MAIN EXPERIMENT

The interaction between the viscoelasticity of the skin booster and the syringe's diameter had a noticeable impact on injection force. An increase in filler concentration corresponded to a higher injection force requirement. Additionally, a clear negative correlation emerged between needle diameter and injection force. We executed a series of five experiments, wherein the exclusion of extreme values—both maximum and minimum—was undertaken. After this exclusion, the mean and SD were computed based on the remaining three data points. A two-tailed *t* test, assuming equal variances, was conducted to compare these forces. The analysis revealed a statistically significant difference between the 34G needles and 33G needles ($P = 0.006$) and between the 33G needles and 30G needles ($P = 0.0039$) at a 95% CI (Fig. 4).

The effect of the inner diameter of the syringe on injection force is depicted in Figure 5. The results demonstrate a positive correlation between the diameter of the syringe and the injection force required to deliver the filler material. Notably, the data indicate that the growth in force conforms to an exponential trend rather than a linear one, as the syringe diameter expands ($P < 0.001$, based on a *t* test assuming equal variances, with a 95% CI).

The impact of needle length on injection force becomes evident as the data show a direct relationship: with an increase in needle length, there is a corresponding increase in the force needed for intradermal injection ($P < 0.001$, *t* test assuming equal variances, at a 95% CI), represented in Figure 6.

DISCUSSION

Intradermal injection is a common drug delivery method, providing direct administration of active ingredients for therapeutic effects. Skin boosters, often low-viscoelastic hyaluronic acid fillers or combinations with various ingredients, fall into two regulatory groups: medical devices and cosmetic products. This study focuses on testing skin boosters approved as medical devices.

Research by Nikolis et al demonstrated hyaluronic acid-based skin boosters' efficacy through micro-droplet intradermal injections, showing positive effects on face, neck, and hands.[6] Another study by Park et al highlighted the benefits of long-chain polynucleotide injections improving skin quality.[7] Combination of hyaluronic acid and polynucleotides was endorsed in a consensus article, suggesting synergetic effects.[5]

This article, inspired by the clinician's experience as the first author with skin booster procedures, explores outcome variations with different injection delivery methods. The Bernoulli principle in fluid dynamics, particularly fluid velocity, plays a vital role in understanding injection protocols and quantify outcomes.

Porcine skin, closely resembling human skin, is commonly used as a model for studying skin physiology, dermatology, and wound healing. Its thickness similarity allows for accurate evaluation of substance penetration. However, differences between porcine and human skin exist, emphasizing the need for validation studies when applying findings to humans.[8–11]

Needle Gauge	Length	Injection Force / 1ml syringe	Injection Force / 3ml syringe
30G	14.7mm (1/2 inch)	12.2N	32.4N
30G	4mm	5.7N	11.3N

* P<0.05 ** P<0.01 *** P<0.001

Fig. 7. The collective impact of various factors, including the inner diameter of the syringe, needle diameter, and needle length, underwent comprehensive analysis in relation to injection force. Specifically, we compared the impact of needles of different lengths (14.7 and 4 mm) in conjunction with syringes of varying diameters, while keeping the needle diameter constant at 30G. Among the four combinations examined, a striking difference was observed when using a 30G 14.7-mm needle with a 3-mL syringe compared with a 30G 4-mm needle with a 1-mL syringe. This resulted in a substantial reduction in injection force, decreasing from 32.4 to 5.7 N, representing a six-fold reduction. These disparities were all statistically significant, as confirmed by paired *t* tests conducted with a 95% CI. Detailed *P* values are presented in the figure. The inner diameters of 1-mL and 3-mL syringes were 6.3 mm and 10.0 mm, respectively.

Our findings, presented in Figure 4, indicate that an increase in filler concentration leads to a corresponding increase in the injection force required. This suggests that a more dilute filler solution, with lower viscoelasticity, would be easier to inject into the dermis. Additionally, an inverse relationship between needle diameter and injection force was observed. Our results demonstrate that larger diameter needles result in a decrease in the force required for injection. Thus, using a needle with a larger diameter facilitates ease of injection into the dermis.

Also, as presented in Figure 5, there was a direct correlation between the diameter of the syringe and the injection force necessary for delivering the filler material. It was found that the increase in force was exponential in nature, as opposed to linear, as the diameter of the syringe increased. Based on these findings, it can be concluded that smaller diameter syringes are preferable for intradermal injections due to their comparatively lower injection force requirements.

Furthermore, as depicted in Figure 6, there was a positive correlation between needle length and the force required for filler injection. Specifically, as the length of the needle increased, the force necessary for intradermal injection was also elevated. Our findings suggest that the use of a shorter needle is advantageous for easier administration of filler in intradermal injections.

The collective impact of various factors, including the inner diameter of the syringe, needle diameter, and needle length, underwent comprehensive analysis in relation to injection force. Specifically, we compared the impact of needles of different lengths (14.7 and 4 mm) in conjunction with syringes of varying diameters, while keeping the needle diameter constant at 30G. Among the four combinations examined, a striking difference was observed when using a 30G 14.7-mm needle with a 3-mL syringe compared with a 30G 4-mm needle with a 1-mL syringe. This resulted in a substantial reduction in injection force, decreasing from 32.4 N to 5.7 N, representing a six-fold reduction. These disparities were all statistically significant, as confirmed by paired *t* tests conducted with a 95% CI. Detailed *P* values are presented in the Figure 7.

Accurate intradermal injection is crucial for the optimal effects of skin boosters. The dermis is a dense, yet thin layer, and any deviation from the proper injection technique, such as injection into the subcutaneous layer or loss of product due to oozing out of the skin, can negatively impact the desired effects. The findings of the present study, as depicted in Figure 2, reveal that subcutaneous injection requires a lower force compared with intradermal injection. This can be attributed to the delicate nature of the dermis, which is thin and dense.[9] To achieve effective intradermal injection, a higher ejection pressure from the needle tip is necessary to penetrate the dermal density. By identifying the conditions that result in the least injection force necessary to achieve the optimal ejection pressure, intradermal injection can be performed effectively with less effort. Previous research by Lee et al established that ejection pressure increases at an exponential rate with respect to injection pressure and demonstrated that injection pressure is proportional to injection force.[12]

It is generally recognized that the viscosity of a skin booster is determined by the amount of hyaluronic acid mixed with it. When assessing the performance of a specific skin booster, it is considered more important to achieve easy and effective injections rather than focusing on the viscosity level of the product. Unlike fillers, skin boosters are not used to maintain the structure after injection, but to ensure that the active ingredients are sufficiently absorbed into the skin.[4] Lowering viscosity may be advantageous in such cases. Even if viscosity is a crucial factor in representing the product's effectiveness, this study proposes more effective injection methods instead of reducing viscosity. These methods may involve adjusting needle length, syringe diameter, and other factors to achieve the desired results.

CONCLUSIONS

To achieve a sufficient ejection pressure to induce dermal detachment through low injection force:

1. The concentration of the skin booster substance must be dilute;
2. The inner diameter of the needle for injection must be large;
3. A syringe with a small diameter should be used;
4. The length of the needle for injection should be short.

When incorporating these four conclusions into actual clinical practice, several useful outcomes can be achieved.

First, mixing noncrosslinked hyaluronic acid or botulinum toxin or lidocaine with skin booster during intradermal injection is an effective treatment strategy. The added benefits of this approach include the antiwrinkle effect of the toxin and the pain-reducing effect of lidocaine, in addition to facilitating the intradermal injection process itself.

Second, the use of a needle with a larger inner diameter is preferable for intradermal injection. However, it should be noted that an increase in needle size may result in increased pain.[13] To mitigate this, the use of a needle with a thinner wall, but with the same gauge, is recommended for more effective intradermal injection.

Third, a syringe with a smaller diameter is more suitable. If the product is contained within a large syringe with a wide diameter, it is advisable to transfer it to a smaller syringe through subdivision. This is particularly relevant in cases where co-injection with botulinum toxin or lidocaine is performed, as noted in the first conclusion. Subdividing after mixing has been found to be an effective strategy.

Fourth, using a short needle is advantageous. According to the Bernoulli principle, the resistance to fluid flow through a tube is proportional to the length of the tube. The results of the authors' experiments, which involved testing needles of different lengths with the same diameter, confirmed this relationship.

The application of the third and fourth recommendations to actual clinical practice results in a notable reduction in injection force. Specifically, when comparing the use of a 30G one-half inch (12.7 mm) needle with a 3-mL syringe to the use of a 30G 4 mm needle with a 1-mL syringe, a decrease in injection force from 32.4 N to 5.7 N was observed, representing a six-fold reduction (Fig. 7).

The significance of this study extends beyond offering practical recommendations for performing intradermal injections. The authors provide a guideline for product design, enabling the development of user-friendly products in the initial stages of production. These results provide valuable information for product manufacturers on how to design effective skin boosters by reducing viscosity, utilizing syringes with small diameters, and incorporating short, thin-walled needles. This not only enhances ease of use but also reduces waste by avoiding unnecessary subdividing or transferring of products. Specifically, the use of large-diameter syringes for skin boosters results in the need for multiple smaller syringes for subdividing and mixing, leading to increased waste of disposable medical devices.

In conclusion, clinicians should take into account optimal conditions that facilitate intradermal injections, thus maximizing the outcomes. Furthermore, manufacturers of skin boosters should formulate the products with decreased viscosity and provide the product in conjunction with appropriate needles and syringes, designed to optimize ease of injection.

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DISCLOSURES

Dr. Seung Min Oh has been a clinical advisor for S.THEPHARM, Seoul, Republic of Korea. Jae Hyuk Lee is an employee of S.THEPHARM Inc. The hyaluronic acid fillers (QT fill fine, S.THEPHARM) were sponsored by S.THEPHARM Inc. All the other authors have no financial interests to disclose.

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