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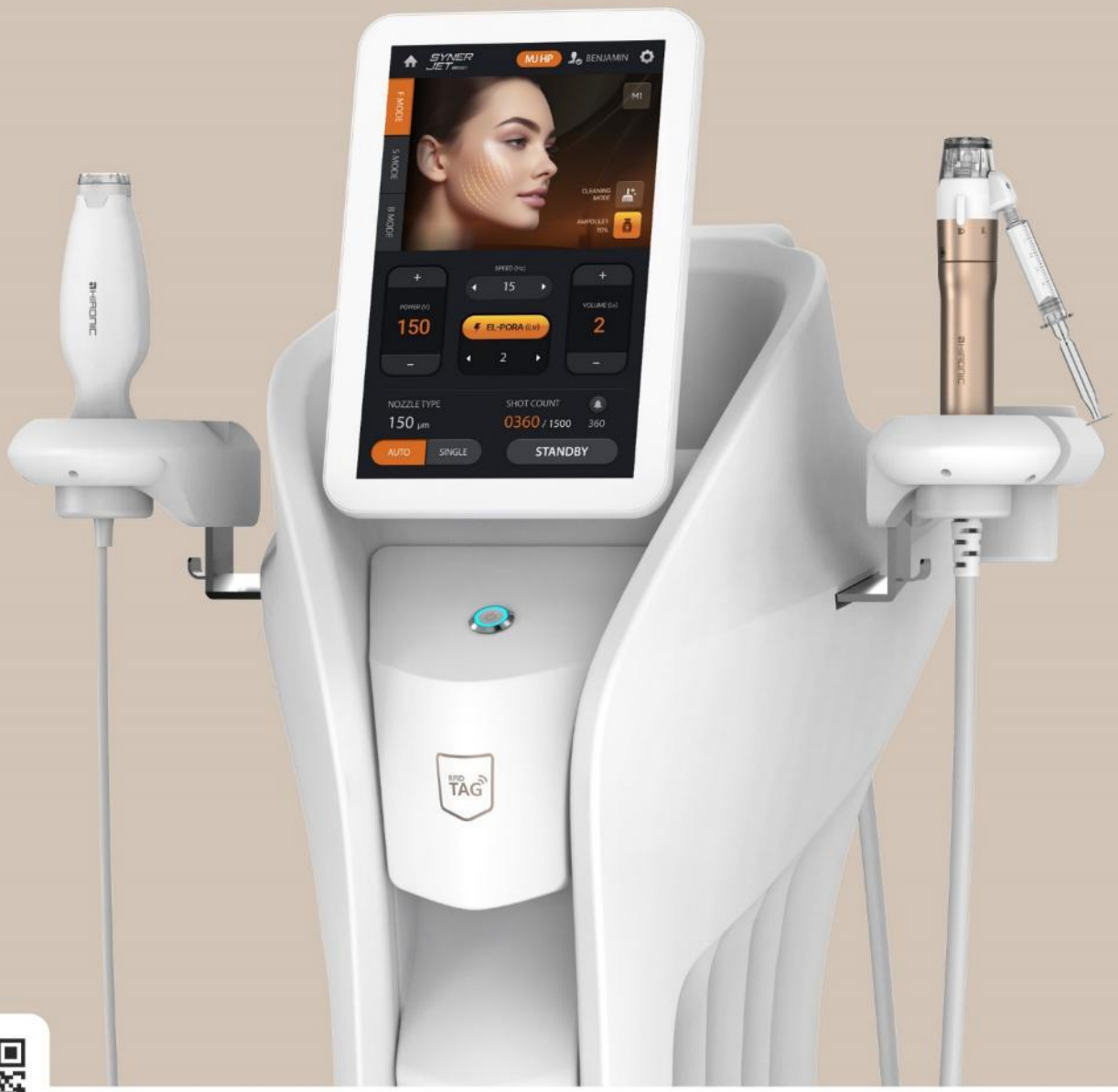
PHYSICIAN'S CLINICAL GUIDE

SYNER JET PRO



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HIRONIC

Three Energies. Powerful Delivery

SYNER™ JET PRO

Physician's Clinical Guide

DISCLAIMER

▶ The treatment guidelines presented in this Physician's Clinical Guide are based on various clinical studies, academic publications, and diverse case reports. The suggested parameters for specific procedures should be adjusted based on individual patient cases. The manufacturer assumes no liability for issues arising from the inappropriate use of the device or excessive treatment.

▶ Prior to using the device, practitioners shall consult the user manual and thoroughly understand the device's proper operation and handling procedures.

▶ A comprehensive treatment protocol should include patient history review and lesion diagnosis during the pre-treatment consultation, the treatment procedure, frequency, anticipated outcomes, potential adverse effects, pre- and post-treatment instructions for both practitioner and patient, patient counseling regarding the aforementioned, selection of appropriate treatment parameters based on the therapeutic objective, post-treatment care, medication prescriptions, and scheduling follow-up appointments.

▶ The indications and parameters described in this guide may be updated based on clinical cases and treatment experiences; therefore, practitioners should refer to the latest insights regarding clinical applications.

▶ The content herein is based on the opinions of healthcare professionals with extensive clinical experience and is recommended for use as a reference during procedures. To enhance proficiency in device operation, a fundamental understanding of the technology and equipment, training, and accumulation of clinical experience are necessary.

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Chapter I.

Overview

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1. Introduction

[1] INTRODUCTION

With age, the human skin generally experiences a reduction in elasticity, leading to wrinkles and sagging. Consequently, various pharmaceutical treatments and functional cosmetics are employed to mitigate these effects and maintain skin firmness. However, the skin serves as a protective barrier against external stimuli and substances, exhibiting impermeability to water-soluble compounds. As such, the mere topical application of functional cosmetics often proves insufficient for effective management.

Dermatological cosmetic procedures necessitate the precise delivery of drugs or active ingredients into the deeper layers of the skin, particularly the dermis. Achieving desired outcomes, such as wrinkle reduction, pigmentation lightening, improved elasticity, and sustained hydration, often requires permeating the skin barrier to reach these deeper layers, as surface application alone is frequently inadequate. The skin, however, is inherently designed to impede the penetration of foreign substances. The outermost layer, the stratum corneum, is characterized by low water content and a dense lipid structure, rendering it highly resistant to the natural passage of high-molecular-weight compounds, water-soluble substances, and ionic species. While this structural feature is advantageous for protecting the body from external pathogens, it poses a significant obstacle to the delivery of drugs for therapeutic or cosmetic purposes.

Initially, needle-based injection techniques were the primary method employed. However, limitations associated with invasive procedures spurred the development of transdermal drug delivery (TDD) technologies as an alternative approach capable of effectively delivering drugs while minimizing invasiveness. The emergence of technologies capable of delivering polymeric or functional ingredients to the dermis without the use of needles has enabled effective and painless aesthetic treatments. Advances in techniques such as electroporation, sonophoresis, iontophoresis, and needle-free jet injection have facilitated the temporary disruption of the skin barrier or the forced introduction of drugs, thereby expanding the range of applicable compounds regardless of their type or molecular size. Compared to injections, these methods offer advantages such as reduced pain and side effects, and a quicker return to daily activities, which is highly appealing to clients who regularly undergo cosmetic procedures. A variety of ingredients, including polynucleotides (PN), hyaluronic acid, antioxidants, vitamins, growth factors, and peptides, can be combined to create customized treatments tailored to specific skin conditions.

As the skin safeguards the body from external irritants and chemicals, it inherently restricts the passage of most external substances. Transdermal drug delivery (TDD) technologies, which employ the application of an electric field (or high voltage) to cells to enhance cell membrane permeability, have therefore become a significant component of the aesthetic market. However, a limitation of these technologies lies in their tendency to induce absorption based solely on frequency output, without adequately considering factors such as skin hydration levels. High-voltage electroporation, which involves the application of voltage for several milliseconds (ms), induces temporary electroporation between skin cell membranes and the stratum corneum. While this method enables the transdermal delivery of macromolecular or non-ionic drugs,

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repeated application can exacerbate skin irritation, necessitating short treatment durations. Pain may also occur, particularly in sensitive facial areas, emphasizing the importance of carefully controlling output and establishing appropriate treatment intervals. Traditional non-invasive drug delivery techniques such as topical application, iontophoresis, and sonophoresis, although capable of penetrating the skin surface, exhibit limited delivery efficacy to the deeper layers of the dermis. Drugs used in TDD are typically limited to lipophilic small molecules with a molecular weight of 500 Da or less. Large molecules, such as hyaluronic acid, polynucleotides (PN), and peptides, struggle to cross the stratum corneum, often remaining on the skin surface without reaching the desired therapeutic depth.

Skin booster procedures aim to improve hydration, elasticity, and skin texture by evenly delivering skin-rejuvenating ingredients such as hyaluronic acid or polynucleotides (PN) into the skin. Traditionally, these substances have been administered through repetitive microinjections using needles. While this conventional needle-based approach offers the advantage of precisely delivering drugs to the desired depth, it can be accompanied by adverse effects such as pain, bruising, swelling, and bleeding. Moreover, patients with a fear of needles may be reluctant to undergo the procedure. Given that many patients seeking cosmetic procedures are particularly sensitive to post-treatment appearance, this invasive method has been a limiting factor in treatment accessibility. Furthermore, the outcome can be influenced by the operator's skill. Inconsistent injection depths or volumes, even when using the same product, can lead to uneven skin surfaces or inconsistent results, as well as potential drug wastage. Consequently, solenoid-based needle-free jet injection devices are increasingly being adopted for skin booster treatments, offering advantages such as controlled dosing, consistent depth of injection, ease of repetitive administration, and reduced pain and discomfort for patients, compared to conventional needle-based techniques.

This technology utilizes a piston driven by an electromagnetic force to rapidly deliver medications into the skin in the form of a highly focused, high-velocity jet. This provides sufficient pressure to penetrate the skin and deliver the drug to the dermal layer without the need for a needle. The process involves energizing a solenoid, which in turn drives a piston to eject the drug solution at high speed. The resulting micro-jet stream penetrates the skin with high pressure, allowing the drug to be delivered to the dermis without a needle. A key advantage of this technology is that it is virtually painless and allows for the repetitive injection of precise amounts of medication at a controlled depth, without the use of needles. This is particularly well-suited for procedures such as skin boosters, where medications need to be evenly distributed across a broad area of the skin at a shallow depth.

The minimal bleeding or bruising associated with this technique also allows patients to resume their daily activities without significant downtime, which is a significant advantage. In addition, the electronic control system enables precise adjustments of injection depth, pressure, and volume, which minimizes operator variability and ensures consistent results across treatments. By eliminating needles, the risk of infection is also reduced, making it a safer option, particularly for areas with thin or sensitive skin. Solenoid-based needle-free jet injection technology is therefore considered an effective method for delivering drugs to the dermis, while addressing the limitations of conventional techniques, and its application is growing in skin

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booster treatments and other cosmetic procedures.

Synerjet pro is a hybrid needle-free injection device that combines a needle-free injection with electroporation, a transdermal drug delivery (TDD) technology, into a single handpiece. This combination reduces drug loss and continuously delivers a consistent amount of medication to the dermal layer. Previously, achieving dermal delivery of skin boosters required needle injections and the associated pain. Furthermore, drug loss, a major drawback of conventional NFID, often necessitated invasive procedures. To overcome these limitations, HIRONIC has developed a proprietary optimized nozzle to minimize drug loss, and a handpiece capable of simultaneous NFID and electroporation, maximizing drug absorption. The following will outline the clinical efficacy of Synerjet pro based on the principles and mechanisms of each technology.

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[2] Skin Structure

The skin, which serves as a protective barrier covering the body, is broadly divided into three layers.

(1) Epidermis

The epidermis is the outermost layer of the skin, acting as the first line of defense against the external environment. It forms a highly impermeable barrier that prevents water loss and protects the body from ultraviolet radiation and the invasion of pathogens. Moreover, melanocytes in this layer produce melanin, the pigment responsible for skin color. As the epidermis is avascular, it receives oxygen and nutrients via diffusion from the underlying dermis. The primary cell types found in the epidermis include keratinocytes, melanocytes, and Langerhans cells.

The stratum corneum, composed of dead cells that we commonly refer to as skin flakes, provides an external protective barrier. The stratum lucidum, an optically transparent layer, is present only on the palms and soles. The stratum granulosum reinforces the skin barrier through the formation of lipids and proteins. The stratum spinosum contains Langerhans cells (immune cells) and activates keratin production. Finally, the stratum basale, the innermost layer, houses stem cells and melanocytes and serves as the starting point for skin regeneration.

(2) Dermis

The dermis, located beneath the epidermis, is the middle layer and constitutes the majority of the skin's thickness. This layer consists of connective tissue and is richly supplied with blood vessels, lymphatic vessels, nerves, sweat glands, sebaceous glands, and hair follicles. The dermis nourishes the epidermis and is abundant in collagen and elastin, elastic proteins that maintain the skin's elasticity and tensile strength. Furthermore, the dermis is firmly attached to the epidermis via the basement membrane, providing structural stability.

The papillary dermis primarily contains blood vessels, sensory nerve endings, fibroblasts, and extracellular matrix (ECM) components such as collagen and elastin. It supports the epidermis, provides nutrients, and mediates sensory functions. The reticular dermis, on the other hand, contains thick collagen fibers, sweat glands, sebaceous glands, hair follicles, and lymphatic vessels, providing structural support, maintaining hydration, and contributing to immune function.

(3) Hypodermis (Subcutaneous Tissue)

The hypodermis, or subcutaneous tissue, is the deepest layer of the skin, primarily composed of adipocytes and loose connective tissue. This layer serves as a connection between the skin and underlying muscles or bones, and it also functions in thermoregulation and shock absorption. This region also provides a pathway for large blood vessels and nerves, serving as an important route for delivering nutrients and stimuli to the

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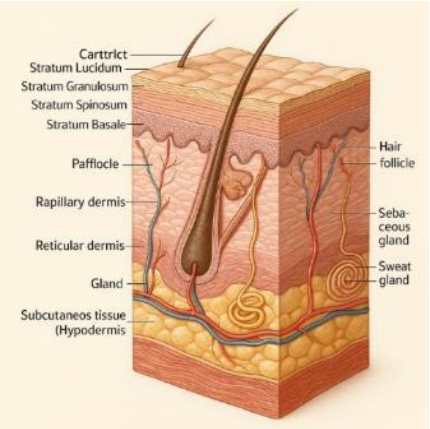
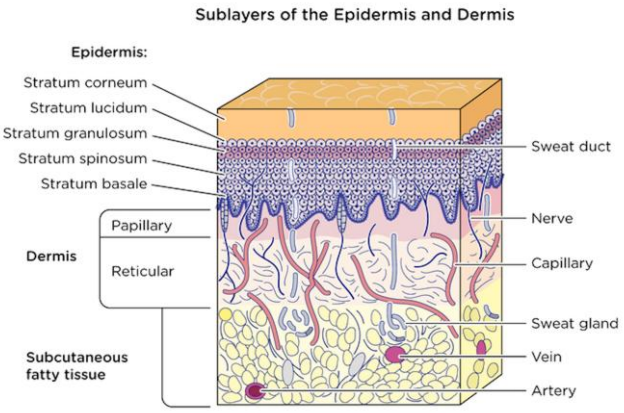
dermis and epidermis. Structurally, it contains both elastin and collagen fibers, providing both flexibility and support.





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2. Needle-Free Injection Device (NFID)

[1] Needle-Free Injection Device: NFID

The history of Needle-Free Injection Devices (NFIDs) spans over 80 years, during which time they have undergone continuous evolution driven by advancements in medical and engineering technologies. Initially developed for efficient military vaccinations and mass immunization campaigns, their application has recently broadened to include self-injection, vaccines, insulin, growth hormones, and aesthetic medicine. As the name suggests, needle-free injection is a technology that delivers drugs without the use of a needle. This method involves spraying medication in the form of an ultra-high-speed jet through a very narrow opening (nozzle), allowing it to penetrate the skin. The drug travels at a ballistic speed (over 100-200 m/s), using its kinetic energy to breach the skin and permeate into the underlying tissue. Devices such as springs, compressed gas, electromagnetic force (solenoids), and piezo actuators are used to generate instantaneous, intense pressure internally. The pressure created propels a piston within the drug chamber, causing the drug to move rapidly and be ejected through micro-nozzles with diameters of 100-200 μm in the form of a high-speed jet that penetrates the skin, delivering the medication to the desired depth (dermis, subcutaneous layer(hypodermis)).

[2] History of NFIDs

(1) Early Development Phase (1940s-1960s)

- Late 1940s:
  - Dr. Aaron Ismach developed the first needle-free jet injector (piston-based) in the United States.
  - This system utilized a high-pressure spring to inject drugs subcutaneously.
  - The goal was to reduce the time required for large-scale vaccinations during wartime and prevent infections.

- 1950s-1960s:
  - Used in large-scale vaccination campaigns by the WHO and the US military medical system for the prevention of infectious diseases.
  - Representative devices: Hypospray, Ped-O-Jet, Med-E-Jet
  - Advantages: Rapid injection speed, elimination of needle-related infection/waste issues
  - Disadvantages: Difficulty in controlling injection depth, risk of cross-contamination, potential for skin damage

(2) Commercialization and Refinement Phase (1970s-1990s)

- Mechanical Jet Injectors began to be commercialized due to technological improvements.
- Spring-based and compressed gas-based devices were representative.
- Limited use for vaccines, steroids, and local anesthetics.

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- However, a WHO report (late 1980s) raised concerns about cross-contamination due to nozzle reuse → The use of multi-dose nozzle devices for multiple patients was gradually discontinued.

(3) Evolution to Single-Dose Devices (2000s-Present)

- Development of next-generation needle-free injectors incorporating single-use cartridges or nozzle designs.
- From this period onward, miniaturized and quantitatively controllable products for various purposes emerged.
- Examples: Biojector®, PharmaJet®, Injex®, ZetaJet™
- Stringent regulations by the US FDA and WHO made cross-contamination prevention a key design criterion.
- Application areas: Insulin, growth hormones, vaccines, botulinum toxin, anti-obesity drugs, etc.

(4) Recent Trends and Technological Advancement (2010s-Present)

- Integration of advanced technologies such as solenoid-based systems, piezoelectric actuation, and micro-electro-mechanical quantitative dispensing systems.
- Enabling painless injections, self-injections, high-viscosity drug delivery, and precise intradermal injection.
- Re-evaluation as a non-invasive and non-traditional vaccine delivery method following the COVID-19 pandemic.
- Increased research on mRNA and DNA vaccine delivery, and non-traditional drug delivery routes.

(5) Current Application Areas

- Medical: Insulin, growth hormones, vaccines, anesthetics, anti-obesity drugs
- Aesthetic medicine: Botulinum toxin, hyaluronic acid, skin boosters, etc.
- Veterinary medicine: Large-scale livestock vaccination (e.g., avian influenza)
- Military/Global Health: Disaster area and border vaccination programs

[3] Operating Principles of Needle-Free Injection Device((NFID)

When an electric current flows through the solenoid coil, a strong magnetic field is generated, rapidly accelerating a magnetic metal piston (also referred to as a projectile or plunger). The accelerated piston strikes the drug chamber, causing the drug to be expelled through micro-nozzles at extremely high velocities. This ejected drug penetrates the skin, reaching the dermis or subcutaneous tissue. NFIDs utilize high pressure to propel the drug (in liquid form) through micro-nozzles as a high-speed jet (exceeding 100–200 m/s). This jet penetrates the skin (including the stratum corneum and dermis) to a specific depth, thereby delivering the drug.

- Electrical Energy → Magnetic Energy → Kinetic Energy (Piston Acceleration) → Fluid Kinetic Energy
- Electrical Signal → Solenoid Activation → Piston Acceleration → Drug Compression → Jet Formation

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through Nozzle → Skin Penetration

- Initiation: Electrical Energy → Magnetic Energy
- Acceleration: Magnetic Field Generation → Drug Compression
- Jet Formation: Piston Acceleration → High-Speed Jet Ejection
- Skin Penetration: Drug Jet → Skin Penetration
- Dispersion: Drug Diffusion into the Dermis or Subcutaneous Tissue

[4] Fluid Dynamics in Needle-Free Injection Devices (NFIDs)

Pressure, often referred to as driving pressure, is the force exerted per unit area, typically measured in Pascals (Pa) or Megapascals (MPa). It serves as the energy source for jet generation, commonly produced via springs, compressed gases (e.g., CO_2, N_2), or electromechanical piston systems. Elevated pressure facilitates deeper penetration and increased jet intensity, whereas lower pressure tends to confine the drug to the epidermis. Consequently, pressure becomes a critical determinant in skin penetration.

Viscosity (μ), denoting a fluid's resistance to flow (or "stickiness"), is quantified in Pascal-seconds (Pa·s) or centipoise (cP). Higher viscosity impedes flow, resulting in diminished velocity at a given pressure and, consequently, reduced penetration. Therefore, low-viscosity solutions are preferred, generally within the range of 1 to 10 mPa·s.

Jet velocity is determined by pressure, flow rate, and nozzle area. A velocity exceeding 100–200 m/s is generally considered necessary for skin penetration. High jet velocity enhances skin penetration, while insufficient velocity results in inadequate penetration and potential dispersion on the skin surface.

Pulse duration refers to the total time the jet is emitted. It requires precise adjustment to ensure accurate penetration within a short timeframe, thereby minimizing thermal and pressure effects on surrounding skin tissues. An excessively short pulse duration can lead to incomplete penetration and backflow.

Orifice diameter (D) is a key factor in regulating flow rate and pressure. Its typically small size, on the order of 100–200 μm, facilitates high-speed jet formation. Increasing the nozzle diameter increases the flow rate at a given pressure but reduces jet velocity. Conversely, decreasing the nozzle diameter can increase velocity but reduces the drug delivery volume. The nozzle length (L) is generally designed to be short to minimize frictional losses.

Surface tension represents the tendency of a liquid's surface to minimize its area. It influences the formation of the jet by inhibiting droplet formation as the liquid exits the nozzle. The phenomenon of a jet breaking up into droplets is termed Rayleigh-Plateau instability or jet breakup.

Inertial force refers to the force that enables the fluid to maintain its existing state of motion, a crucial

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factor for penetrating the skin. The kinetic energy of the drug shall overcome skin resistance to traverse the epidermis and dermis and ultimately reach the subcutaneous layer.

Jet penetration condition is defined by F ≥ skin resistance force or P ≥ penetration threshold pressure, indicating the need for sufficient kinetic energy for the drug to penetrate the skin. A plunger, actuated by a solenoid, generates an instantaneous pressure.

$$E_k = \frac{1}{2}mv^2$$

$$P=\frac{F}{A}$$

> F: Plunger acceleration force generated by the solenoid (N)
> A: Cross-sectional area of the plunger (m^2)

Bernoulli's principle, also known as the law of conservation of energy for pressure, velocity, and position, can be used to derive the jet velocity from pressure. Upon impacting the skin surface, the jet fluid shall overcome skin tension and resistance to penetrate the stratum corneum and subsequently reach the dermis/hypodermis. As the drug passes through the nozzle, its pressure decreases and its velocity sharply increases in accordance with Bernoulli's principle.

$$P + ½\rho v^2 + \rho gh = \text{Constant}$$

$$P= \frac{1}{2}\ \rho \cdot v^2$$

$$v=\frac{\sqrt{2P}}{\rho}$$

> P: Internal pressure of the syringe (Pa), inertial force
> ρ: Drug density (kg/m^3, typically 1000 kg/m^3 based on water)
> v: Jet velocity immediately before reaching the skin

Pressure loss in the micro-nozzle depends on the viscosity and the length-to-diameter ratio of the nozzle.

$$\Delta P=\frac{128\mu LQ}{\pi D4}$$ (Hagen–Poiseuille equation)

> ΔP: Pressure loss
> L: Nozzle length
> Q: Flow rate
> D: Nozzle diameter

Needle-free injection devices (NFIDs) minimize nozzle length or employ a tapered structure to efficiently

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increase flow velocity. The nozzle shape, often described by the taper angle, converges the spray flow, stabilizing the jet formation. A structure with a wide inlet and a narrow outlet can further enhance the injection force.

The Reynolds number (Re), which represents the ratio of inertial forces to viscous forces, indicates that the drug flow within the NFID is generally located in the transition region between laminar and turbulent flow. Generally, Re >> 4000 indicates turbulent flow, where inertial forces dominate viscous forces. A higher Reynolds number implies that inertial forces are more dominant than viscous forces, leading to increased skin penetration. Furthermore, it suggests that injection velocity is even more crucial for high-viscosity drugs.

$$Re = \frac{\rho v D}{\mu}$$

ρ: Fluid density
v: Injection velocity
D: Nozzle diameter
μ: Viscosity

The Weber number (We), representing the ratio of inertial forces to surface tension, allows for the evaluation of jet stability. A higher Weber number indicates that a straight, non-atomized jet formation is more easily achieved. For skin penetration, a high Weber number (>1000) is essential for stable, straight jet formation.

$$We = \frac{\rho v^2 D}{\sigma}$$

[4] Key Features of Needle-Free Jet Injection Devices

(1) Minimized Pain and Reduced Injection Phobia

These devices deliver drug in a high-velocity jet (100-200 m/s or higher) penetrating the epidermis and reaching the dermis or subcutaneous tissue without the use of a needle. This feature makes them particularly suitable for individuals with a fear of injections, including children, the elderly, and those with sensitive skin. The absence of a needle significantly reduces pain or discomfort, facilitating a less stressful treatment experience.

(2) Reduced Risk of Infection and Injury

The elimination of needles removes the potential for cross-contamination associated with their reuse. Furthermore, needle injuries and related infection risks are virtually eliminated.

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(3) Decreased Risk of Skin Trauma

Traditional injections can often result in bruising, marking, or bleeding. Needle-free injection minimizes these side effects by avoiding physical puncture of the skin.

(4) Precise and Controlled Dosage Delivery

By adjusting the device's pressure or duration settings, medications can be delivered precisely to desired depths, such as intradermally or subcutaneously. The ability to precisely control injection parameters based on the treatment area and medication characteristics is a significant advantage.

(5) Compatibility with Diverse Drug Formulations

These devices are capable of delivering a wide range of drug formulations, including low-viscosity liquids, highly viscous substances, and fine powders. Current applications span various fields, including the delivery of botulinum toxin, hyaluronic acid, peptides, vaccines, insulin, and growth hormones.

(6) Variable Depth of Application

Drug can be delivered to specific layers of the skin (e.g., intradermal, subcutaneous) by adjusting the jet pressure. Nozzle diameter, injection pressure, and pulse duration can be modified based on the intended application.

(7) Enhanced Environmental and Hygienic Profile

The absence of needles eliminates the issue of contaminated sharps waste disposal. Many devices also incorporate single-use nozzles or cartridges, promoting ease of hygiene management and further reducing the risk of infection.

[5] Needle-Free Jet Injection Technologies

Technical Approach	Description	Advantages	Disadvantages
① Mechanical Spring-based (Spring-powered)	The compressed spring Push the plunger to inject the drug	Simple structure, low cost	Fixed input energy, Difficulty controlling shallow injection layer, Nonuniform acceleration,

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			pressure attenuation occurrence (Hook's Law), Low repeatability
② Mechanical Gas-based (Gas-propelled)	Compressed air / CO_2 / drug propulsion / N_2 combustion gas	High speed/permeability, Pressure adjustability, High pressure is available, Theoretically, high-speed jets	High splashback occurrence, Difficulty controlling distribution, Some system combustion by-products, Temperature sensitivity, Recharge Problem
Mechanical Combustion-based (Chemical gas)	Injection into gas produced by combustion reaction	High pressure implementation	The stench, Validation complex, a disposable tendency
① Electromagnetic Piezo-based	piezo element	Precision speed control, Suitable for small/epidermal injection, Reduce splashback	Amplifier required (30–150V, 4A), Difficulty injecting bulk, Concerns over device enlargement
② Electromagnetic Lorentz force-based (Lorentz forced)	Voice coil Piston acceleration with magnetic field + current	High-viscosity drugs can also be injected, Can be equipped with feedback control, Noise reduction, High control, Can be miniaturized	Current control required, High cost, Structural complexity, Difficulty in miniaturization
Laser-based (Laser-powered)	Er:YAG Ultrafine Jet Fluid Formation	Precision control, Target delivery	Complex structure, High price
Shock wave-based (Shockwave)	Dispensing drugs with ignited explosive force	Non-contact delivery, High speed	Safety concerns, Structural complexity

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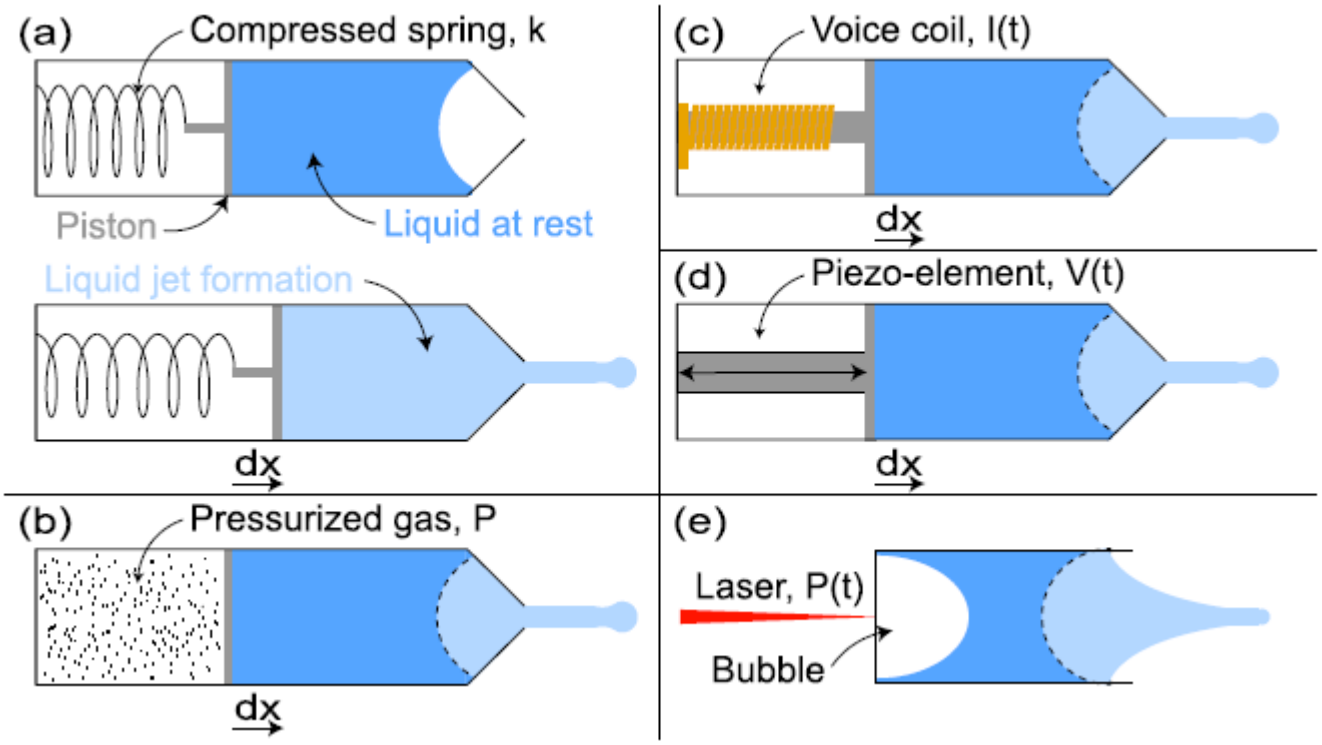

(a) Compression Spring Method: The upper illustration depicts the pre-ejection stage, while the lower illustration shows the ejection stage in progress. The stored energy in the spring is released, propelling the piston and ejecting the liquid.

(b) Compressed Gas Method: The pressure of a compressed gas is utilized to drive a piston, ejecting the liquid in a jet form.

(c) Lorentz Force/Voice Coil Method: An electromagnetic force is employed to move a piston, thereby ejecting the liquid. The voice coil is an electromagnetic device analogous to the operating principle of a loudspeaker.

(d) Piezoelectric Method: A piezoelectric element deforms upon electrical stimulation, driving a piston to eject the liquid.

(e) Laser-Induced Vapor Bubble Method: A focused jet is generated through flow focusing, achieved by locally generating a vapor bubble using a laser. This method obviates the need for a nozzle.

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3. Skin Booster

[1] Classification of Polymers Used in Skin Regeneration

Polymers employed for skin regeneration can be broadly categorized into natural and synthetic materials. Within each category, further classifications are based on structural characteristics, resulting in diverse biocompatibility profiles and functionalities.

(1) Natural Polymers

Natural polymers, derived from substances found within living organisms, offer advantages such as high tissue compatibility and minimal immunogenicity. Key classifications include:

■ Polysaccharide

- Hyaluronic Acid (HA): Exhibits exceptional moisture retention capabilities and is highly effective in restoring dermal volume.
- Chitosan: Possesses antibacterial and biodegradable properties, making it suitable for wound healing applications.
- Cellulose and Dextrin: Characterized by high stability and employed as delivery vehicles.

➢ Proteins

- Collagen: Serves as a fundamental component of the skin's supportive structure, contributing to elasticity and promoting regeneration.
- Gelatin: A hydrolyzed form of collagen, exhibiting enhanced absorption rates.
- Fibrin: Involved in hemostasis and tissue regeneration processes.
- Fibroin: A silk protein demonstrating cell adhesion properties and the ability to induce regeneration.

➢ Nucleotides

- Polydeoxyribonucleotide (PDRN): A DNA fragment that induces inflammation suppression and tissue regeneration.
- Polynucleotide (PN): Effective in promoting cell growth and improving skin condition.
- Defibrotide: A substance reported to exhibit vascular stabilization and tissue protection effects.

(2) Synthetic Polymers

Synthetic polymers allow for structural modification tailored to specific purposes, leading to their widespread use in drug delivery, tissue augmentation, and collagen stimulation.

■ Biodegradable Polymers

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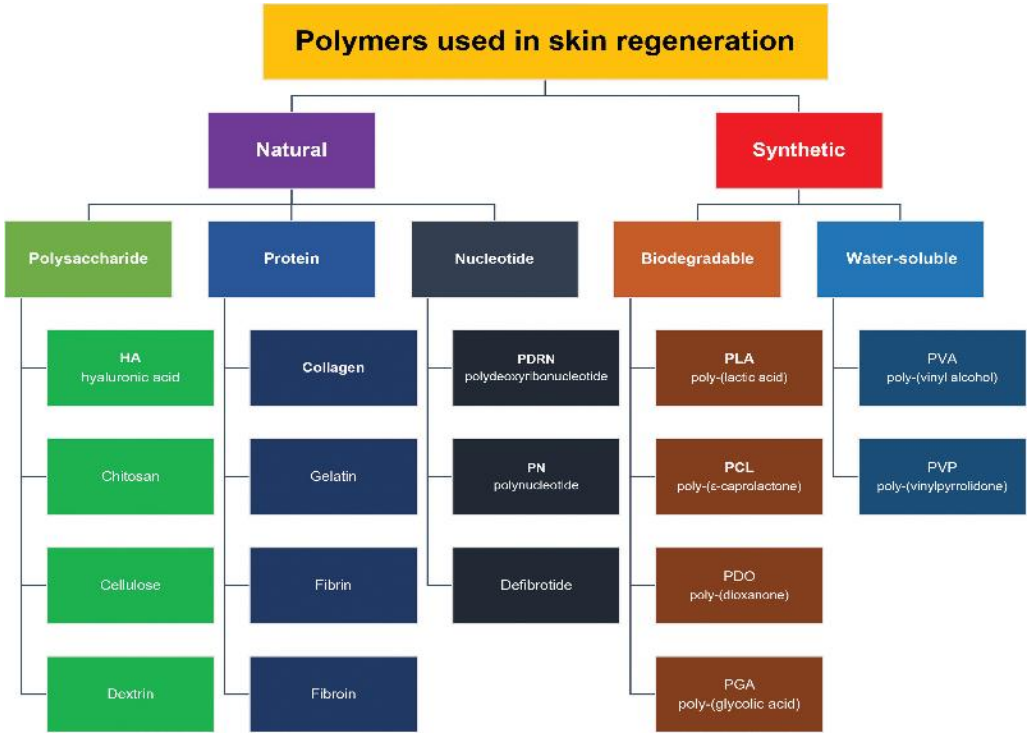
- Poly-lactic acid (PLA): Undergoes gradual degradation in vivo, stimulating collagen production.
- Polycaprolactone (PCL): Exhibits a slow degradation rate, making it suitable for long-term volume maintenance.
- Polydioxanone (PDO): Primarily used in silhouette lifts and lifting threads, inducing collagen remodeling.
- Polyglycolic acid (PGA): Characterized by rapid degradation and is commonly used in absorbable sutures.

➢ Water-soluble Polymers

- Polyvinyl alcohol (PVA): Possesses excellent biocompatibility and viscoelasticity, leading to applications in drug delivery systems.
- Polyvinylpyrrolidone (PVP): Its stability and ease of mixing make it a frequent component of drug delivery systems.



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[2] Natural Polymers

■ Hyaluronic Acid(HA)

Hyaluronic acid is a substance found in various connective tissues within the human body, particularly abundant in the extracellular matrix (ECM) of the dermal layer of the skin. It is a type of glycosaminoglycan (GAG). Originally extracted from bovine vitreous humor, hyaluronic acid is a constituent of human connective tissues. As a GAG prevalent in the dermal ECM, it exhibits exceptional water-binding capacity, capable of attracting up to 1,000 times its weight in water. When injected into the skin, it not only provides hydration but also maintains the stability of the fibrous structure and enhances skin adhesion. Direct injection of HA draws moisture into the surrounding tissues, increasing the skin's hydration level. This increased hydration leads to secondary effects such as pore reduction and a radiant, dewy skin appearance. Its physiological roles within tissues include promoting skin recovery and modulating immune responses. It has potential applications in cancer diagnostic research and contributes to wound healing and tissue regeneration, while its anti-inflammatory effects help suppress inflammation.

The effects of hyaluronic acid injection on the skin include an increase in soft tissue volume, filling sunken areas, and improved skin hydration. It stimulates collagen and elastin production, strengthening the skin structure. This leads to increased skin elasticity and regenerative capacity, and higher aesthetic scores (cosmetic satisfaction). It reduces wrinkles and scars, resulting in overall cosmetic improvements such as refined skin texture and enhanced radiance.

HA formulations are broadly classified into non-crosslinked and crosslinked varieties.

(1) Non-Crosslinked Hyaluronic Acid(HA)

- Key Products: High Inj, etc.

Typically used in hydro radiance(hyaluronic) injections, it comprises 100% pure HA and is highly safe, even for intra-articular injections. When injected into the skin, HA attracts and retains moisture within the tissue, increasing the skin's hydration. The injected HA is naturally degraded within the body over a certain period.

(2) Crosslinked Hyaluronic Acid(HA)

- Key Products: Juvederm VOLUX, Restylane Vital Light, etc.

This formulation employs chemical bonding (crosslinking) between HA molecules to slow down the degradation rate. Each manufacturer possesses unique crosslinking technologies, resulting in extended degradation times. It is injected into the deep dermis for lifting or volume augmentation purposes and exhibits sufficient viscoelasticity to maintain its shape, allowing its use as a dermal filler. When used for skin

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booster applications, the injection depth within the skin layer is carefully considered during product development.

*Glycosaminoglycan (GAG): A disaccharide compound composed of glucuronic acid and N-acetylglucosamine (NAG).
*ECM: Dermal Extracellular Matrix

■ Polynucleotide(PN)

Polynucleotide (PN), a biomaterial derived from salmon testes DNA, is utilized for tissue repair and hydration purposes. It has gained prominence as an injectable agent for skin regeneration and anti-aging in recent years. Key characteristics of PN include: It is sourced from salmon testes DNA and serves as a high-molecular-weight biomaterial for tissue restoration. PN is indicated for the temporary amelioration of superficial wrinkles around the eyes and mouth. Due to limited absorption via topical application, it is exclusively administered via injection. Classified as a high-grade medical device, it is effective when injected into the dermal layer. It is a single substance, devoid of protein antigenicity, and exhibits a low potential for allergic reactions. Its high molecular weight and viscosity may induce a sensation of physical foreignness or discomfort during injection. Optimal results are typically achieved with a regimen of three or more treatments administered at 2-3 week intervals. Common treatment areas include fine lines around the eyes, thin skin on the eyelids and perioral region, tear troughs, nasolabial folds, sagging cheeks, and sunken areas below the jawline or cheekbones. PN provides hydration, resulting in a natural increase in skin volume, dermal thickening, and a reduction in fine lines. Its cell regeneration properties offer potential anti-aging benefits, leading to overall improvements in skin texture, elasticity, and thickness. It is particularly suited for addressing subtle wrinkles that are often unresponsive to botulinum toxin. Unlike fillers, it provides a natural anti-aging solution without artificial volume enhancement.

< Comparison of PN and PDRN >

Classification	PN	PDRN
Extraction Site	salmon testis	a semen of salmon
Chemical Structure	long DNA polymer	a short DNA polymer
Average olecular weight	>1000kDa	About 350kDa
Functions	Water absorption, supply of nucleotides, serving as tissue support	Anti-inflammatory, cell proliferation, vascular production
Clinical Effects	Materials for skin regeneration, cartilage/joint regeneration, bone formation, tissue repair	Tissue regeneration, wound healing, corneal production
Field of Application	Restoring tissues and improving skin environment	Acute tissue damage healing

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➢ Key products: Rejuran, etc

- Rejuran Series (PharmaResearch)

(1) Rejuran Healer

- Key Ingredient: PN approximately 2 mg/mL
- Indications and Effects: Comprehensive skin rejuvenation and anti-aging effects; improvement of wrinkles, sensitive skin, and redness; addresses complex skin concerns.
- Viscosity: 20~200 Pa·s
- Characteristics: A representative multi-type skin booster aimed at improving fine lines, skin texture, and skin tone.

(2) Rejuran HB Plus

- Composite Ingredients: Rejuran Healer + Hyaluronic Acid (HA) + Lidocaine
- Effects: Regulates skin moisture balance and provides soothing effects.
- Viscosity: 13 ± 8 Pa·s
- Characteristics: A moisture-enhanced skin booster formulated for dry and sensitive skin.

(3) Rejuran S

- Key Ingredient: PN approximately 10 mg/mL
- Indications and Effects: Specifically for scar treatment; promotes tissue regeneration after injury and improves skin in areas of hardened tissue.
- Viscosity: 20~200 Pa·s
- Characteristics: Characterized by its high viscosity and firm texture, making it suitable for treating localized deep damage, such as acne scars.

(4) Rejuran I

- Key Ingredient: PN approximately 1 mg/mL
- Indications and Effects: Specifically designed for the under-eye area; improves fine lines and dark circles, providing a softer and more natural volume compared to hyaluronic acid fillers.
- Viscosity: 20~200 Pa·s
- Characteristics: Formulated with a low-irritant formula suitable for the delicate skin around the eyes.

■ Collagen

Collagen, a natural polymer protein, is a key material widely utilized in tissue engineering and skin regeneration. It is used as a skin substitute, tissue filler, and adjuvant for regenerative induction.
As a naturally derived polymer and an intrinsic component of tissues, it exhibits excellent biocompatibility. Based on its natural distribution within skin tissue, it demonstrates high affinity with the tissue even upon

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external supplementation. While its mechanical properties are weak and its biodegradation is rapid, leading to lower immediate volume retention compared to HA fillers, it offers the advantage of high biological regeneration induction capacity. Due to its biocompatibility, flexibility, evasion of immune responses, and controllable degradation rate, interest in intradermal collagen injections has recently been increasing.

- Type I Collagen: Improves skin elasticity, thickness, and texture.
- Type III Collagen: Facilitates wound healing and regeneration / Provides structural support for Type I collagen.

A representative product is Laetigen® (Dmed).

- Type I collagen-based supplement used to protect damaged ligaments, tendons, muscles, and fascia, or for the recovery of surgical incision sites.
- Collagen Content: Approximately 2.7~3.3 mg/mL based on a 3.0% concentration.
- Hydroxyproline (8~14%), Tyrosine (≤ 2%), Cysteine (≤ 0.5%), Glycine (≥ 20%)
- Viscosity: 100 ~ 1,000 cP → Lower viscosity than typical fillers, but provides adequate fluidity for intradermal injection.

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[3] Synthetic Polymers

Various biodegradable polymers, including poly-L-lactic acid (PLLA), poly-DL-lactic acid (PDLLA), polycaprolactone (PCL), and polydioxanone (PDO), are employed as collagen-stimulating fillers to induce collagen synthesis and promote tissue regeneration. The majority of these are available in lyophilized powder form and require reconstitution with sterile saline or distilled water prior to use. However, certain products, particularly those based on PCL, are offered in pre-filled syringes containing a gel formulation.

■ PLA(Polylactic Acid)

Polylactic acid (PLA) is a thermoplastic, aliphatic polyester derived from starch extracted from plants such as corn and sugarcane, making it an environmentally friendly polymer material. Exhibiting excellent biocompatibility and biodegradability, PLA is predominantly used in the field of nonsurgical rejuvenation. Upon injection into the subcutaneous tissue, PLA stimulates collagen production over time, leading to a gradual increase in volume. This mechanism is considered a method to potentially achieve effects similar to those of facial fat grafting. The stimulated fibroblasts induce extracellular matrix (ECM) remodeling, primarily involving collagen type I, resulting in a natural and long-lasting volumizing effect over time. Regenerative benefits, such as improved skin texture and increased dermal thickness, can also be expected.

While sharing the same chemical formula ($C_3H_6O_3$), PLA exists in multiple forms with differing physical properties due to variations in their stereochemical structure (three-dimensional arrangement). These structural differences manifest as mirror images, classifying them as stereoisomers with distinct properties. Despite possessing the same molecular composition, PLLA and PDLA are challenging to physically blend homogeneously due to their structural differences, represented by a mirror-image relationship in their molecular structure, and their varying degrees of crystallinity.

PLLA (Poly-L-lactic acid)	It consists of L-type lactic acid and is semi-crystalline Used as a key ingredient in FDA-approved fillers for long-term volume recovery, effective for approximately 24 months or longer Ex) Sculptra
PDLA (Poly-D-lactic acid)	D-type lactic acid is difficult to break down in biological tissues and is not used well for direct medical use
PDLLA (Poly-D,L-lactic acid)	A mixture of L-type and D-type lactic acid, mostly composed of amorphous In combination with HA, improve elasticity + induce collagen stimulation at the same time, with fewer pain and side effects and natural results Ex) LENISNA

■ PCL (Polycaprolactone)

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Polycaprolactone (PCL) is a biodegradable polymer exhibiting a semicrystalline structure and classified as an aliphatic polyester. It is insoluble in water and characterized by slow degradation over several months to years due to the presence of ester linkages. This property enables PCL to induce collagen regeneration and improve skin elasticity over extended periods following intradermal injection. Due to its excellent biocompatibility, PCL elicits minimal rejection responses within human tissues and undergoes natural degradation within the body, ensuring biodegradability. Exhibiting nontoxicity and ductility, PCL contains ester linkages, rendering it susceptible to hydrolysis and enabling gradual decomposition and safe absorption in vivo. Its particulate form is processed into smooth, uniform microspheres, which reduces injection pain and enhances dispersibility. Following injection into the dermis, PCL undergoes gradual degradation, stimulating fibroblasts and inducing collagen type I-centered regeneration. While it can provide immediate volume augmentation akin to hyaluronic acid (HA) fillers, PCL is better suited for longer-term structural improvements, making it well-suited for procedures where both immediate and sustained effects are desired.

A representative product is ELLANSE, which comprises:

- Composition: Polycaprolactone + Phosphate-buffered saline

- Viscosity: 180~230 Pa·s

- Intended Use: Improvement of facial wrinkles and volume loss, induction of long-term tissue regeneration via injection into the dermis or subcutaneous layer.

■ PLLA (Poly-L-Lactic Acid)

Poly-L-Lactic Acid (PLLA) is a biodegradable polymer filler that stimulates natural collagen production within the skin, gradually restoring volume. Unlike hyaluronic acid (HA) fillers, which provide immediate volume, PLLA exhibits its effects progressively over time. It induces an immune response via macrophage stimulation, which in turn promotes collagen biosynthesis by fibroblasts. Derived from L-type lactic acid obtained from plants such as corn and sugarcane, PLLA is characterized by its hydrophobic interior and high stability as a semicrystalline particle.

PLLA promotes the production of various types of collagen, including type III collagen. However, excessive inflammatory reactions may lead to the formation of nodules or granulomas. PLLA particles gradually absorb moisture at the injection site, stimulating immune cells. During the initial 1–3 weeks, inflammatory mediators increase due to the immune response; thereafter, from the third month, the number of inflammatory cells decreases, with a concomitant increase in fibroblast conversion. Gradual stimulation of fibroblasts leads to peak collagen formation at 6 months, ultimately resulting in increased skin elasticity and volume restoration. Post-treatment swelling is mostly a temporary phenomenon caused by the water used for dilution and typically subsides within a few days. The structural support provided by the newly formed collagen can

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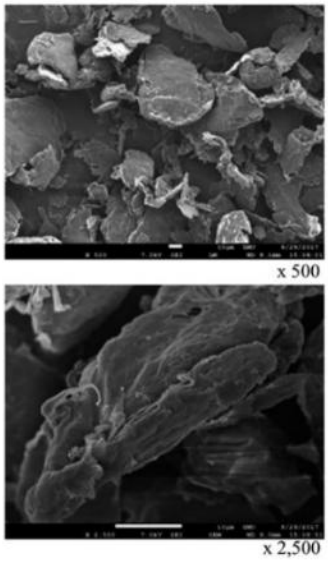
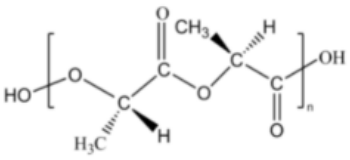
ensure long-term sustainability, lasting for 1–2 years.

A prominent example of PLLA is Sculptra.

Initially approved by the FDA for the treatment of lipoatrophy in HIV patients, its cosmetic applications expanded starting in 2009. It was introduced in South Korea in 2011 and is currently used to improve moderate to severe facial wrinkles and volume loss in adults. Injections should be administered exclusively into the subcutaneous layer; strict intradermal injections are contraindicated due to the potential of complications when injected too close to the skin surface. Caution is particularly advised when treating thin areas such as the jawline, forehead, and temples. Calcified or fibrous nodules may persist long-term, necessitating careful administration. Adequate time (at least 6 hours) for reconstitution is crucial to ensure even dispersion of the PLLA particles. As Sculptra primarily aims to stimulate collagen production, its application should be distinguished from that of volume fillers, warranting a different treatment approach.





Poly L Lactide ,

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■ PDLLA (Poly-D,L-Lactic Acid)

Poly-D,L-Lactic Acid (PDLLA) is an amorphous polymer synthesized by copolymerizing PLLA and PDLA in a 1:1 ratio. Its structurally amorphous nature results in a rapid reaction rate and high degradation rate, rendering it suitable as a skin booster ingredient that stimulates collagen production upon intradermal injection. PDLLA functions as microparticles within the skin after injection. Compared to PLLA, PDLLA exhibits a softer texture and enhanced biodegradability, resulting in reduced swelling and inflammatory responses immediately post-procedure. Hyaluronic acid (HA) serves as a carrier, ensuring stability upon intradermal injection and promoting enhanced diffusion. This approach simultaneously induces a physical filling effect and biological collagen regeneration, finding versatile applications ranging from superficial wrinkles around the eyes, nasolabial folds, and cheeks, to the improvement of deeper tissue structures. Depth modulation is achievable by adjusting particle size and concentration, concurrently stimulating regeneration of the entire facial layer and enhancing structural volume while providing tissue carriage and collagen stimulation effects. Key products include LENISNA 50 and LENISNA 200.

LENISNA 50	LENISNA 200
PDLLA 42.5mg+ HA 7.5mg= 50mg Particle size: 20–50 μm (24 μm) Small particles, injected into the skin layer at the right concentration, effective	PDLLA 170mg+ HA 30mg= 200mg Particle size: 40~80㎛ (51㎛) Larger particle size, effective in increasing volume by performing tissue depth procedures at higher concentrations
① Reducing skin pores ② skin scar treatment ③ Relief of skin wrinkles and fine wrinkles	① natural volume increase of bumpy forehead ② Improved cheek sagging ③ relief of deep skin wrinkles ④ Increased skin elasticity

LENISNA treatment is recommended for individuals who require improvement of fine, superficial wrinkles caused by loss of skin elasticity; desire natural skin volume enhancement without the pronounced volumizing effect of fillers; need to improve skin tone and texture; seek treatment for areas difficult to improve with elasticity enhancements, such as the back of the hands or knees; require treatment for shallow scars or acne scars; aim to alleviate blemishes, redness, and hyperpigmentation; or need to improve enlarged pores. The duration of the effect typically lasts for 6 to 12 months, and optimal results are reported with 2 to 3 repeated treatments at 6-week intervals. The injected moisture contributes to initial volume and hydration, while PDLLA particles act within the dermis to improve the dermal structure and promote collagen production, ultimately increasing skin elasticity, reducing fine wrinkles, and improving skin texture. Over time, volume gradually increases, inducing a natural and translucent skin transformation. Temporary injection site bruising and skin unevenness may occur but will resolve spontaneously. Pain at the injection site is generally comparable to mild injection pain.

To prevent nodule formation, which can occur with excessively superficial or excessive volume injections,

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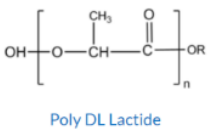
adequate dilution and injection into the appropriate skin layer are recommended. Compared to Sculptra, LENISNA may provide less initial/immediate volume due to its smaller particle size and morphology, but this can be addressed with repeated treatments at 4- to 6-week intervals.

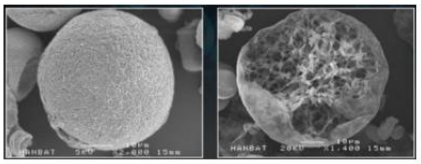
Differences between PLLA and PDLLA (Differences between Sculptra and LENISNA):

- PDLLA has a lower glass transition temperature than PLLA.
- PDLLA has no melting point.
- PDLLA has a higher transparency.
- PDLLA is more rapidly biodegradable in vivo compared to PLLA.
- PDLLA particles are smaller, smooth, and spherical, facilitating dispersion within the tissue.

Therefore, due to these differences, LENISNA, which contains PDLLA, can be used as a skin booster.



Poly DL Lactide


PDLLA 전자현미경 사진

■ PDO (Polydioxanone)

Polydioxanone (PDO) is a polymer composed of biodegradable ester bonds, initially developed for use as a surgical suture material. Its excellent biocompatibility, minimal tissue irritation, and rapid degradation rate have led to its widespread adoption in various non-surgical wrinkle reduction and skin rejuvenation procedures. Possessing a highly polar structure, PDO exhibits high stability and readily undergoes hydrolysis. It is naturally absorbed within the tissue and degrades completely without leaving residues. While previously employed extensively in the form of cogged threads and mono-threads for thread lifting, recent advances have led to the development of microsphere formulations, expanding its applications as a filler alternative and skin booster. Following injection, the microspheres maintain their spherical shape without external stimulation and degrade naturally, conferring Ultracol superior biodegradability compared to PLLA or PCL.

- Representative Products: Ultracol 100 / Ultracol 200
- Composition: PDO 75%, SCMC (Sodium Carboxymethyl Cellulose) 25%
- Viscosity: 1,000 ~ 1,400 cP (@25℃)

The intended use is to improve bilateral facial volume loss. It achieves skin tissue regeneration through physical filling and restoration, after which the moisture is absorbed, and the PDO particles disappear from the tissue through biodegradation. Treatments are typically administered at intervals of at least 3 to 4 weeks, with complete degradation usually occurring after 7 to 8 months. While the duration of effect is shorter compared to Sculptra or LENISNA, it presents a significantly lower risk of nodule formation and a stable natural degradation process. Viscosity varies depending on the hydration method; manual or natural

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hydration is recommended to avoid bubble formation due to the CMC component, as mechanical hydration may induce this. Following hydration, sufficient time (typically 6 hours or more) should be allowed for complete particle dispersion. When re-administering the treatment, care should be taken to avoid overlapping with previous injection sites, paying attention to layering and areas of application. The inclusion of air bubbles during the hydration process can lead to uneven pressure during injection, potentially causing skin irritation.

Main Ingredients	Key Products	Major Treatment Areas	Purpose of the Procedure	The Texture	Main Ingredient
PLLA (Poly-L-lactic acid)	Sculptra	Blusher cheeks, nasolabial folds	Long-term volume increase, improved skin texture, collagen type 1 centered regeneration	Lyophilized powder	PLLA
PDLLA (Poly-D,L-lactic acid)	LENISNA	Area of decreased elasticity, wrinkles, turned-off cheeks, front cheeks, under eyes	Skin texture improvement, collagen type 1 regeneration, hyaluronic acid-based natural volume	Lyophilized powder	PDLLA + HA
PCL (Polycaprolactone)	Ellansé	Scallops, cheekbones, nasolabial folds	Immediate volume + long-term collagen regeneration, improved facial contour	Gel-form suspension	PCL 30% + CMC 70%
CaHA (Calcium Hydroxyapatite)	Radiesse	Disappearance around the mouth, decreased elasticity, deep wrinkles	Improve skin texture + immediate volume effect, collagen type 1/3/vascular regeneration, long-term stability Excellent reliability	Gel-form suspension	CaHA30% + CMC 70%
PDO (Polydioxanone)	ULTRACOL (Ultra V)	Decrease in elasticity	Collagen regeneration, skin texture	Lyophilized powder	PDO+SCMC

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			improvement		

■ Amino Acids-based Boosters

Recently, amino acid-based regenerative injectables have garnered significant attention as an advanced evolution from conventional hyaluronic acid (HA)-centric skin boosters. These injectables operate via a mechanism of action that involves stimulating fibroblast activity, thereby promoting collagen synthesis, particularly the production of Type III collagen, and concurrently inducing angiogenesis, leading to the remodeling of the extracellular matrix (ECM) structure. They are indicated for cases requiring improvement of facial photoaging, skin texture, elasticity, and density, as well as comprehensive reorganization of the ECM. While traditional HA skin boosters primarily focus on hydration and inducing temporary radiance, amino acid-based skin boosters represent a treatment strategy centered on cellular metabolism activation and tissue regeneration. In essence, this represents an expansion beyond simple moisturization into the realm of anti-aging and regenerative-focused biological therapies. Key amino acids include Proline, Glycine, Lysine, and Leucine, with low molecular weight HA also serving as a major component.

■ Glycerol

Contemporary skin boosters are gaining prominence not only for their capacity to deliver hyaluronic acid (HA) to the skin, but also for incorporating auxiliary components designed to maximize its efficacy. In particular, the inclusion of hydrophilic ingredients such as glycerol, mannitol, and polysaccharides enhances moisture retention, antioxidant properties, and extracellular matrix (ECM) stability. A strategy employed to augment the delivery of hyaluronic acid (HA) to the dermis and prolong its residence time within the skin involves the addition of glycerol, mannitol, and polysaccharides. Glycerol functions to enhance hydration, soften the skin, and improve dermal moisture retention. Mannitol serves as a potent antioxidant, inhibiting the oxidative degradation of HA. Polysaccharides maintain viscoelasticity, improve hydration, stabilize the ECM, and protect the skin barrier. Notably, mannitol also inhibits HA degradation by hyaluronidase, which can significantly extend the duration of HA post-treatment. While HA alone provides temporary hydration, moisturization, and increased viscoelasticity, the combination of HA and hydrophilic additives enhances moisture retention, mitigates oxidative stress, protects the skin barrier, and potentially leads to long-term improvements in skin texture and tissue stabilization. In contrast to previous hyaluronic acid skin boosters that primarily offered temporary hydration, this combination represents an advancement towards long-lasting moisturization and antioxidant-based anti-aging therapies.

■ CaHA (Calcium Hydroxyapatite)-based Filler

Calcium hydroxylapatite (CaHA)-based fillers, sometimes referred to as calcium fillers, comprise a product category characterized by the mechanism of action of calcium hydroxylapatite (CaHA) combined with

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carboxymethyl cellulose (CMC). A prominent example is Radiesse. These fillers typically consist of 30% CaHA and 70% CMC gel.

The CaHA particles possess a uniform spherical microparticle morphology, with an average diameter ranging from 25 to 45 μm, approximating 40 μm. They directly stimulate fibroblasts, inducing the production of Collagen Type I and III, which constitute over 90% of skin collagen. Acting as a scaffold, they stretch fibroblasts, thereby activating their function. This stimulation enhances fibroblast metabolism, leading to increased collagen production and the promotion of angiogenesis. Through interaction with fibroblasts, the synthesis of collagen, elastin, and proteoglycans is upregulated. The CaHA microspheres, composed of the mineral components calcium and phosphate, are broken down and eliminated via the kidneys over a period of 9-12 months. Ultimately, the injected components are entirely resorbed, leaving behind only the newly synthesized collagen, resulting in a natural aesthetic outcome.

The CMC gel serves as a carrier, protecting the CaHA particles from external impact and facilitating their absorption and dispersion upon injection. It persists for an initial period of 6-8 weeks before undergoing natural degradation. It exhibits antibacterial, antioxidant, and bactericidal properties.

These fillers demonstrate efficacy in increasing skin thickness and improving elasticity in age-related thinning skin on the back of the hands and are suitable for mitigating superficial wrinkles in areas subject to frequent movement, such as the perioral region and nasolabial folds. While effective in enhancing elasticity in the neck, they are not indicated for addressing prominent submental fullness (double chin).

- Collagen Type I: Improves skin elasticity, thickness, and texture.
- Collagen Type III: Supports tissue repair and provides structural support for Collagen Type I.
- Elastin*: Enhances skin elasticity and firmness.
- Proteoglycans*: Replenish moisture and improve skin firmness.
- Angiogenesis*: Facilitates blood supply and nutrient delivery.

■ Complex Skin Boosters

Complex skin boosters are developed with the aim of activating skin regeneration from multiple angles by combining various regenerative ingredients rather than relying on a single component. They are designed to move beyond simple hydration, focusing on restoring the function of the skin structure itself and promoting long-term health.

The main constituents typically include hyaluronic acid (HA), vitamins A, C, and E, antioxidants such as ferulic acid and lipoic acid, and amino acids (AAs). Unlike conventional skin boosters that primarily consist of single ingredients (e.g., HA, amino acids), complex skin boosters can simultaneously target skin structure improvement, physiological stability, and anti-aging prevention. They are particularly suitable for photoaged skin, age-related dermal thinning, and dry skin with diminished elasticity. Furthermore, they can be used as

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a foundational treatment or in combination with other procedures to potentially achieve synergistic effects.

This multi-component formula, designed to maximize overall skin regeneration, features ingredients that act synergistically to address complex skin issues. By providing multifaceted action, including antioxidation, collagen production, ECM stabilization, improved skin radiance, and enhanced hydration, they offer an integrated solution for various skin concerns rather than merely resolving a single problem, ultimately helping to maintain an optimal balance for skin health.

Enhancement of fibroblast function is expected to improve skin elasticity and restore ECM synthesis capacity, while the promotion of ECM protein synthesis should increase the production of Type I collagen and elastin. Activation of cellular metabolism accelerates the skin regeneration cycle and improves turnover. Furthermore, suppression of oxidative stress reduces cell damage caused by free radicals, potentially delaying aging.

In Korea, most are registered as cosmetics and should be used in conjunction with MTS (Microneedling Therapy System) or laser combination therapy at the discretion of a physician. Key products include NCTF135(a.k.a. Chanel Shot), Jalupro(a.k.a. Milan Shot or Prada Shot). growth factor-based injections, and exosomes(Cellapy and Benev Baby Shots).

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4. Electroporation

[1] Electroporation

Electroporation is a physical drug delivery technique that employs short, high-voltage pulses of electrical current (ranging from microseconds to milliseconds) to temporarily alter the structure of the lipid bilayer of cell membranes or the stratum corneum (SC) of the skin. This alteration enables the permeation of water-soluble molecules and macromolecules (such as drugs, DNA, and peptides) into cells or the dermis. The stratum corneum, the outermost layer of the skin, acts as a formidable barrier, characterized by a thickness of approximately 15–20 μm, an electrical resistance of 20–200 kΩ·cm², a breakdown voltage of 75–100V, and a continuous arrangement of approximately 100 lipid lamellar bilayers. Consequently, water-soluble substances, macromolecular drugs, and charged molecules exhibit minimal permeation via simple diffusion. When the voltage drop across the SC exceeds 30V, the rigid structure is physically altered, creating a direct pathway for delivery. While conventional transdermal drug delivery is limited to low-molecular-weight, lipophilic substances, electroporation facilitates the passage of macromolecules, such as proteins, peptides, DNA, and RNA, through the skin. The quantity and rate of drug delivery can be controlled by adjusting the intensity, duration, and number of electrical pulses, a feature highly advantageous for personalized medicine. Electroporation can be implemented using only electrodes and a pulse generator, resulting in low equipment configuration and maintenance costs, coupled with technical simplicity. For example, timolol maleate, used in glaucoma treatment, has been reported to exhibit a five-fold increase in skin permeation when electroporation is applied. Water-soluble substances, macromolecules, and charged molecules that are normally impermeable via conventional transdermal patches can permeate the skin when electroporation is utilized.

[2] Biological Effects of Electroporation

(1) Enhanced Permeability of the Stratum Corneum (SC)

Electroporation involves the application of short, high-voltage electrical pulses, typically ranging from 100 to 1500 V/cm, to the skin, leading to the formation of transient aqueous pores within the intercellular lipid bilayers of the stratum corneum. These pores exist only while the electric field is maintained, facilitating the transdermal delivery of external substances, after which they rapidly self-seal. While the stratum corneum normally exhibits a high resistance of approximately 20 kΩ·cm², electroporation results in an increase in conductivity by more than two orders of magnitude. This induced permeability enables the transdermal delivery of highly hydrated polymers, hydrophilic drugs, and non-ionic drugs, a process that can be achieved without the need for injections or microneedles, allowing for deeper penetration into the skin. Consequently, components that are normally difficult to absorb, such as high molecular weight compounds, water-soluble substances (hydrophilic substances), or electrically neutral substances (non-ionic substances), can be delivered to the deeper layers of the skin.

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(2) Alterations in Cell Membrane Structure

The cell membrane consists of a phospholipid bilayer with a thickness of approximately 110 nm. When the transmembrane voltage (ΔΨm) induced in the cell membrane by an electrical pulse exceeds 0.2 to 1.0 V, it can surpass the dielectric strength of the membrane, resulting in the formation of nano-scale electropores through the alignment of water molecules and hydrogen bonding. The creation of these minute pores in the cell membrane due to electrical stimulation provides a pathway for direct entry of substances into the cell. This approach facilitates the efficient intracellular delivery of various active agents, such as polynucleotides (PN), hyaluronic acid, vitamins, and peptides.

> Electric Field Calculation: $\Delta\Psi m \approx 1.5 \cdot E \cdot r \cdot \cos\theta$ (r: cell radius, E: applied electric field, θ: angle)
> Pore Size: Several nm to tens of nm, adjustable depending on pulse conditions
> Reversible vs. Irreversible EP: Electroporation predicated on cell survival typically employs pulses of <1 ms. Higher energy levels (particularly >1000 V/cm, >10 ms) carry the risk of cell necrosis.

(3) Induction of Cell Activation and Regeneration

Electrical stimulation activates calcium channels (Ca^{2+} channels) within skin cells. This influx of calcium into the cells triggers signaling pathways that promote skin regeneration. This action stimulates fibroblasts in the dermis, promoting collagen production and growth factor secretion, thereby initiating the skin's inherent regenerative and rejuvenating processes.

> MAPK/ERK Pathway Activation: Promotes transcription of Collagen I, III, Elastin, etc. in fibroblasts
> NF-κB Pathway: Regulates the expression of anti-inflammatory/immunomodulatory factors (e.g., IL-10, TGF-β)
> ROS Response: Limited generation of Reactive Oxygen Species may occur from the electrical stimulation itself, counteracted through the expression of antioxidant genes.

(4) Collagen and Elastin Production Enhancement

The active ingredients (PDRN, PN, HA, Peptides) delivered to the dermis via electroporation stimulate fibroblasts within the skin, thereby promoting the synthesis of collagen and elastin. This contributes to improved skin elasticity, reduction of fine lines, and restoration of volume, playing a crucial role in achieving firm and healthy skin.

> Increased TGF-β1 expression → Enhanced Type I collagen synthesis
> Decreased MMP-1 expression → Inhibition of ECM degradation
> Increased synthesis of Fibronectin, Decorin, and Elastin
> → Reorganization of tissue structure and restoration of elasticity

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(5) Anti-inflammatory and Skin Barrier Improvement Effects

By facilitating the transdermal absorption of hydrophilic/ionic drugs, electroporation allows for the efficient delivery of antioxidant and anti-inflammatory substances (Vitamin C, Tranexamic acid, Glutathione) that are otherwise difficult to reach the dermis through simple topical application. This helps to reduce inflammation within the skin and soothe irritated skin. It is particularly effective for skin with pigmentation, blemishes, and redness, and strengthens the skin barrier, increasing its resistance to external stimuli.

> Vit C (Ascorbic acid): Ionized at pH 3-4, but able to overcome the skin barrier with electroporation (EP)
> Tranexamic acid: Minimal skin barrier penetration with topical application; enhanced melanin biosynthesis inhibition with concurrent EP

(6) Skin Aging Improvement and ECM Remodeling

Active ingredients (PN, HA, Peptides, etc.) introduced into cells via electroporation induce the reconstruction of the extracellular matrix (ECM) within the skin. As the structural components supporting the skin are reorganized, skin texture becomes smoother, fine lines are alleviated, and hydration is improved. Consequently, an overall improvement in skin aging can be expected.

> ECM remodeling: Regulation of Collagen I/III ratio, Increased GAGs
> Skin texture improvement: Decreased TEWL, Increased epidermal thickness, Enhanced dermal-epidermal junction structure
> Wrinkle reduction: Increased collagen density in the dermis, Reduced fine lines

(7) Maximizing Transdermal Drug Delivery (TDD) Performance

Generally, the molecular weight of molecules that can be absorbed through the skin is limited to below 500 Da. However, with electroporation technology, even large molecules such as hyaluronic acid and PN can be delivered non-invasively without injections. As a result, it is gaining attention as a needle-free drug delivery method and is highly beneficial in the aesthetic medicine field.

> Delivery of substances with molecular weights of 10,000 Da or more is available
> No influence from molecular charge → Applicable to both ionized and non-ionized drugs
> Reduced time to reach therapeutic concentrations → At least 10 times faster than passive diffusion
> Reproducibility ensured: Standardization of voltage, pulse number, and duration is available_

[3] Principal Applications of Electroporation (EP)

(1) Drug Delivery Applications

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Electroporation facilitates the efficient delivery of substances that are otherwise difficult to permeate the skin or tissues, by temporarily creating pores in the cell membrane. A wide array of substances can be delivered using this technique, including small molecule drugs, fluorescent dyes, vitamins, peptides, proteins, DNA, or RNA, irrespective of their size or properties. Notably, electroporation operates through a dual mechanism involving electrophoresis (material migration under an electric field) and diffusion through aqueous pores, enabling the delivery of high molecular weight substances, which typically exhibit poor skin permeability, to deeper layers of the skin. By carefully adjusting electrical pulse parameters, such as voltage, frequency, and duration, it is available to design optimized permeation pathways for target drugs.

Examples: Timolol (for glaucoma treatment), benzoic acid (preservative), plasmid DNA (for gene therapy experiments, etc.)

(2) Medical Applications

Electroporation is employed in cancer therapy under the name Electrochemotherapy (ECT). This technique transiently increases cell membrane permeability, allowing anticancer drugs to enter cells more effectively. A significant advantage of ECT is its ability to deliver drugs selectively to localized tumors while minimizing systemic toxicity. This targeted approach reduces side effects and enhances therapeutic efficacy. Bleomycin is a representative drug used in ECT.

Nucleic acids such as DNA and RNA are challenging to introduce into cells due to their size and charge. EP is frequently employed as a physical gene delivery method for introducing these molecules into cells, with extensive applications in vaccine delivery, gene editing, and RNA therapeutics research.

Furthermore, electroporation enables the localized delivery of drugs for treating chronic conditions such as inflammation and pain, thereby minimizing systemic exposure and maximizing the drug's effect on the target site. For instance, it can be used to selectively deliver drugs to areas affected by arthritis or neuropathic pain, maximizing therapeutic benefits while minimizing adverse effects.

(3) Cosmetic and Dermatological Applications

Electroporation offers a non-invasive alternative to traditional mesotherapy, which involves injecting drugs using needles. Without puncturing the skin, electroporation can deliver active ingredients, such as hyaluronic acid, vitamin C, and antioxidants, to the deeper layers of the skin. This approach is particularly suitable for clients with sensitive skin or a fear of injections.

Electroporation is also used for wrinkle reduction and skin rejuvenation. When electroporation devices are equipped with rotating handpieces or massage functions, patients can experience comfortable stimulation without pain, which stimulates collagen production and improves skin elasticity. Applications extend beyond

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the face to include areas such as the abdomen, upper arms, and thighs for treating stretch marks or loss of elasticity. Compared to laser or radiofrequency devices, electroporation often entails minimal downtime, contributing to its popularity.

Electroporation is generally well-tolerated due to its relatively painless nature and ability to induce relaxation during the procedure, resulting in high patient compliance, particularly among elderly individuals and those with sensitive skin. Post-treatment irritation or erythema is minimal, and the procedure is considered safe for repeated treatments.

[4] Applications of Electroporation in Cosmetic Procedures

In applications aimed at skin brightening and pigmentation reduction, ingredients such as tranexamic acid, vitamin C, and glutathione are effectively utilized. These compounds help to suppress melanin production or alleviate post-inflammatory hyperpigmentation, while simultaneously promoting a brighter and more even skin tone through their antioxidant properties. In particular, when delivered to the dermal layer in sufficient concentrations via electroporation, more pronounced improvements can be expected compared to conventional topical application.

For the improvement of acne scars, growth factors (EGF, bFGF, TGF-β) and polynucleotides (PN) are commonly employed. These substances induce the reconstruction of damaged dermal tissue and stimulate fibroblast activity, thereby promoting the remodeling of scar tissue. Electroporation provides a pathway for the effective delivery of these high-molecular-weight compounds, and synergistic effects have been reported when used in conjunction with platelet-rich plasma (PRP) or microneedle therapy systems (MTS).

In anti-aging treatments, PN, PDRN, hyaluronic acid, and various peptide components are used. These agents restore the physiological functions of cells within the dermis and stimulate the production of collagen and extracellular matrix (ECM) components, thereby mitigating wrinkles and restoring skin elasticity. PDRN and PN, in particular, directly promote skin cell regeneration and recovery; therefore, when combined with electroporation, a significant regenerative effect can be anticipated even through non-invasive means.

For the purpose of skin hydration and barrier reinforcement, ingredients such as amino acid complexes, ceramides, and hyaluronic acid (HA) are primarily utilized. These compounds reduce transepidermal water loss (TEWL) and restore the lipid structure of the damaged stratum corneum, thereby enhancing the skin's defense against external irritants. Electroporation enhances the permeability of these hydrophilic, high-molecular-weight compounds, aiding in the improvement of the skin's overall barrier function.

In applications targeting hair growth stimulation and scalp treatment, ingredients such as IGF-1, PRP, and minoxidil are employed. Applying electroporation to the scalp can induce increased blood flow around the hair follicles and stimulate follicular cells, thereby facilitating the transition of follicles from the telogen

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(resting) phase to the anagen (growth) phase. The advantages include a deeper penetration depth of the drugs compared to conventional topical application and reduced irritation.

[5] Advantages and Limitations of Electroporation (EP) Procedures

■ Advantages

(1) Non-invasive drug delivery: Electroporation facilitates the delivery of active compounds into the deeper layers of the skin via brief electrical pulses, eliminating the need for needles. This makes it a viable option for patients who are averse to invasive procedures and offers the significant advantage of treatment without scarring or downtime.

(2) Delivery of diverse substances regardless of molecular size and charge: This technique can be applied to a wide range of substances, including high-molecular-weight materials (PN, HA), ionized substances (Vitamin C, tranexamic acid), and non-ionic substances (peptides, antioxidants). It is a versatile physical delivery method, independent of the drug's characteristics.

(3) Treatment extending to the dermis and deeper layers: With its ability to deliver substances deeply and the adjustable pulse intensity and duration, electroporation allows for precise targeting of drug delivery to specific tissues. This enables the resolution of complex issues, such as dermal regeneration, pigmentation reduction, scar treatment, and anti-aging.

(4) Feasibility of repeated treatments without scarring: Electrical stimulation is temporary and causes minimal epidermal damage, making it suitable for continuous management via regular treatment sessions. Patient satisfaction tends to be higher compared to needle-based procedures.

■ Limitations and Precautions

(1) Variability in absorption efficiency based on skin condition: The efficiency of current flow and ingredient penetration can vary depending on factors such as stratum corneum thickness, skin resistance, and the balance of oil and moisture. This can lead to variations in treatment outcomes.

(2) Potential for discomfort due to electrical stimulation: Patients may experience mild tingling or irritation during the procedure due to the electrical stimulation. Those with sensitive skin may report discomfort depending on the pulse intensity and duration, necessitating a pre-treatment test or adjustment of the output intensity.

(3) Temporary pore dilation requiring post-treatment pore management: Electrical stimulation can temporarily widen pores. The sebaceous glands and tissues surrounding pores along the path of the

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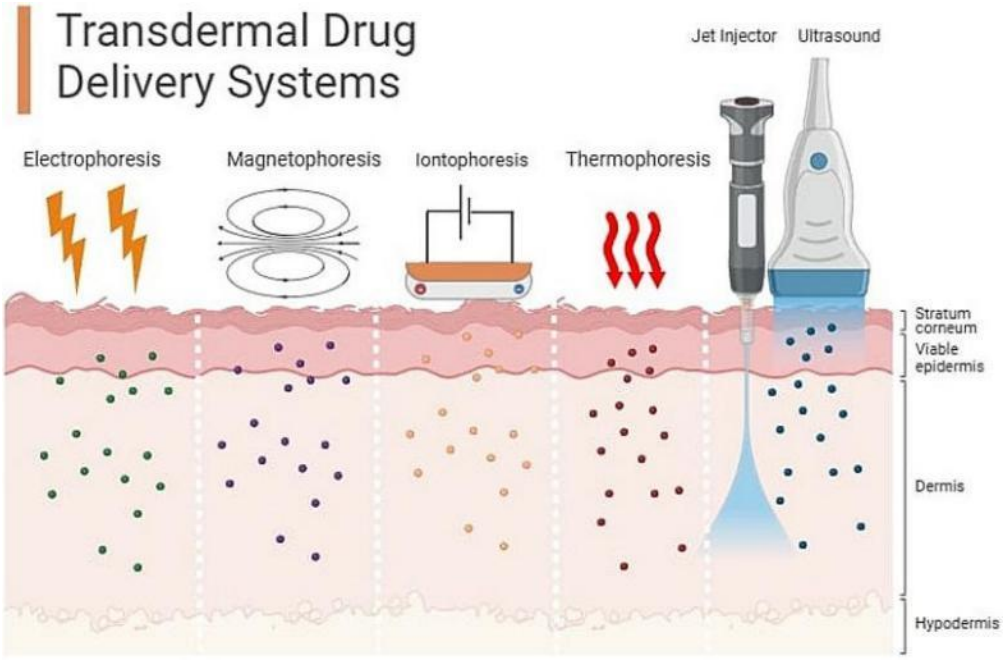
electrical pulses may be stimulated, leading to a rare, temporary increase in sebum production or pore enlargement.

(4) High equipment costs and the need for regular maintenance: Given that the precision of the device is crucial for accurate electrical pulse control, maintaining equipment performance and verifying electrode condition are essential. The replacement cycle for consumables, such as electrode pads, shall also be managed.

(5) Excessive or high-intensity treatments may burden the skin: Repeated electrical stimulation may lead to erythema, temporary hypersensitivity, and inflammatory reactions in some patients. Therefore, adjusting the treatment interval and intensity is imperative.



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5. Plasma

[1] Plasma

Plasma, often referred to as the "fourth state of matter," is an energy state created by ionizing a gas. This process results in a substance containing electrons, positive ions, neutral particles, ultraviolet (UV) radiation, and other components. Common examples of plasma include lightning, auroras, and neon signs.

Cold atmospheric plasma (CAP) is, as the name suggests, plasma generated at a "cold" temperature under "atmospheric" pressure. Unlike typical plasmas, which are extremely hot, CAP is maintained at a relatively low temperature, typically between 30 and 45 degrees Celsius, making it safe for human use. This low temperature prevents skin burns, eliminating pain. Furthermore, plasma's potent sterilizing effect minimizes the risk of infection, and its non-invasive application can enhance the absorption of high molecular weight compounds by stimulating the skin. CAP offers the advantage of synergistic effects when combined with conventional treatments such as laser therapy or drug administration. However, excessive electrical stimulation or prolonged exposure can damage cells, necessitating careful adjustment of exposure time and intensity. Some individuals with sensitive skin may experience erythema or irritation, requiring tailored conditions based on the application site and skin condition. For brevity, cold atmospheric plasma will be referred to as cold plasma henceforth.

Cold plasma is generated by applying electricity to a gas, causing it to ionize and transition into the plasma state. The specific energy components that interact with the skin can vary depending on the type of gas used and the method of electrical stimulation. Gases such as air, argon (Ar), helium (He), or mixtures thereof are commonly employed, with the type of gas influencing the species and concentration of reactive species produced. For example, helium tends to generate a gentler, more stable plasma, while argon produces a plasma with relatively higher energy. Electrical energy can be delivered in various forms, including radio frequency (RF), microwave, high-voltage alternating current (AC), and direct current (DC). Furthermore, operation in continuous or pulsed modes allows for adjusting the stimulation intensity and frequency according to the therapeutic objective.

Rather than being a simple air discharge, cold plasma comprises a complex mixture of physical and chemical elements with diverse biological activities. When these components interact with the skin, they elicit cellular responses, reduce inflammation, and promote tissue regeneration, resulting in various biological effects. Reactive oxygen and nitrogen species (RONS) regulate the intracellular redox state, suppressing inflammatory responses and promoting tissue regeneration. Key reactive oxygen species (ROS) include ozone (O_3), hydrogen peroxide (H_2O_2), hydroxyl radical (•OH), and superoxide anion (O_2^-), which contribute to oxidative stress, cell signaling, and antimicrobial activity. Major reactive nitrogen species (RNS) include nitric oxide (NO), nitrogen dioxide (NO_2), and peroxynitrite ($ONOO^-$), playing roles in immune modulation, inflammation suppression, and vasodilation. The generated ultraviolet (UV) radiation triggers biological responses such as stimulating epithelial cells, inducing subtle DNA alterations, and enhancing antibacterial

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effects. Electrons and positive ions contained in the plasma generate a micro-electrical field on the tissue surface, altering the cell membrane potential and thus promoting permeability or cell responses.

Cellular responses are contingent upon the duration of exposure (dosage). Shorter exposure times to cold plasma generally exert positive effects on cell activity, while longer exposures can inhibit cell function or induce cell death. In particular, short exposures of less than one to two minutes tend to promote cell proliferation and wound healing. Conversely, prolonged exposure of three to five minutes or longer tends to impair cell function or induce apoptosis. This dose-dependent characteristic necessitates precise control of exposure conditions based on the therapeutic objective. Fibroblasts are particularly sensitive to cold plasma. These cells play a crucial role in wound healing and collagen production within the dermis. Prolonged exposure of fibroblasts to cold plasma can reduce the expression of integrin proteins, impairing cell migration. However, very short exposures of approximately 5 to 15 seconds have been shown to promote fibroblast migration and healing responses. Ultra-short, subtle stimulation may be the most effective condition for fibroblasts, leading to increased expression of genes related to inflammation and immune responses. In normal skin cells exposed to cold plasma, genes involved in inflammatory regulation and tissue regeneration, such as IL-8, TGF-β1/2, and β-defensin, are upregulated. These changes in gene expression are directly linked to establishing an antibacterial environment, regulating inflammation at wound sites, and promoting tissue regeneration. In particular, β-defensin is an antimicrobial peptide that enhances the skin's immune defense. Mechanistically, the PPAR-γ pathway may be involved. Some research suggests that cell migration and regeneration responses induced by cold plasma may be related to the activation of PPAR-γ (Peroxisome proliferator-activated receptor gamma), a transcription factor. This pathway can be induced by increased intracellular ROS, ultimately contributing to increased cell motility and accelerated wound healing.

[2] Biological Effects of Cold Plasma

(1) Induction of Oxidative Stress

Cold plasma interacts with oxygen, nitrogen, and moisture in the air to generate various reactive oxygen species (ROS) and reactive nitrogen species (RNS). These collectively known as RONS, are produced outside the cell and can traverse the cell membrane, leading to oxidative stress within the cell. Cancer cells, which typically exhibit a weaker antioxidant defense system (e.g., GSH, SOD) compared to normal cells, are particularly susceptible to cold plasma. This heightened sensitivity can selectively induce cancer cell death. While low concentrations of RONS can modulate intracellular signaling, high concentrations can induce apoptosis through damage to DNA, proteins, and lipids.

(2) Gene Expression Regulation and Epigenetic Modification

Exposure to cold plasma can upregulate the expression of genes involved in wound healing (e.g., IL-6, IL-8, TGF-β1/2) in treated tissues. Furthermore, cold plasma can induce epigenetic changes, such as DNA methylation and histone acetylation, influencing the expression of genes that regulate cell survival, migration,

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and differentiation. In cancer cells, epigenetic regulation can be harnessed to reactivate tumor suppressor genes or inhibit cell proliferation and migration through microRNA modulation.

(3) Mitochondrial Dysfunction and Induction of Apoptosis (Mitochondria-Mediated Apoptosis)
RONS generated by cold plasma can disrupt the mitochondrial membrane potential (ΔΨm), leading to the release of cytochrome c into the cytoplasm. Subsequently, alterations in the ratio of Bcl-2 family proteins, alongside activation of the caspase cascade, trigger the apoptotic pathway. This mitochondria-mediated pathway can induce cell death independently of external stimuli.

(4) Cell Cycle Arrest and Induction of Senescence
The effects of cold plasma on the cell cycle are dose-dependent. High doses of cold plasma can arrest the cell cycle at the G2/M checkpoint, promoting tumor cell death. Conversely, low doses can induce cellular senescence, thereby inhibiting cell proliferation. This process involves cell cycle regulatory genes such as p53 and p21, and is accompanied by a decrease in Cyclin B1 and CDK1.

(5) Immunomodulation and Induction of Anti-cancer Immune Response
Cold plasma can induce the release of damage-associated molecular patterns (DAMPs) (e.g., HMGB1, ATP, calreticulin) from damaged cells, which promotes the maturation of antigen-presenting cells (APCs) and dendritic cells (DCs), as well as the activation of T cells and NK cells. This leads to immunogenic cell death and can shift the tumor microenvironment from an immunosuppressive to an inflammatory state, thereby inducing an anti-cancer immune response.

(6) Antimicrobial Action and Biofilm Eradication
Cold plasma effectively eliminates various pathogens, including multidrug-resistant (MDR) bacteria, by disrupting bacterial cell membranes or oxidizing DNA. It can even eradicate biofilms, providing a solution for infections that are difficult to control with conventional antibiotics. This action relies on physical and chemical sterilization mechanisms independent of antibiotics, positioning cold plasma as a promising alternative technology to antibiotics.

(7) Tissue Regeneration and Promotion of Wound Healing
Cold plasma accelerates tissue regeneration by inducing angiogenesis and promoting fibroblast migration and proliferation. It also enhances collagen synthesis and facilitates epithelial cell remodeling, leading to rapid recovery in chronic wounds, skin ulcers, and burns. The underlying mechanisms involve increased expression

[3] Medical and Dermatological Applications of Cold Plasma:

(1) Wound Healing

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Cold plasma stimulates skin cells (keratinocytes, fibroblasts) and immune cells at the wound site to induce tissue regeneration. In particular, reactive oxygen and nitrogen species (RONS) generated by the plasma promote angiogenesis, the formation of new blood vessels, and increase oxygen supply to the wound area. These changes can convert chronic inflammation to an acute state, which aids in promoting the healing of delayed wounds. Due to these effects, cold plasma can be effectively used for conditions such as diabetic foot ulcers, pressure ulcers, post-surgical wound infections, and refractory chronic wounds. Indeed, some clinical reports indicate accelerated wound recovery within 2 to 3 weeks, along with a reduction in both infection rates and pain.

(2) Antimicrobial Effect

Cold plasma possesses the ability to physically and chemically eradicate various microorganisms, including bacteria, viruses, and fungi. Reactive species produced by the plasma directly oxidize and structurally damage bacterial cell membranes, proteins, and DNA. It can also effectively eliminate bacteria resistant to antibiotics, such as MRSA. Notably, plasma can disrupt biofilm structures formed by bacteria, making it a potent tool against chronic infections that are difficult to treat with conventional disinfectants or antibiotics. Furthermore, unlike antibiotics, plasma is not affected by antibiotic resistance genes, making it a promising alternative treatment for patients with antibiotic allergies or infections unresponsive to antibiotics.

(3) Skin Cancer Treatment

Cold plasma can selectively damage the DNA of cancer cells and induce apoptosis (programmed cell death). This primarily occurs through the mitochondrial pathway, activating protein pathways that suppress cancer cell survival (e.g., Bax/Bcl-2, caspases). Moreover, it stimulates immune cells, altering the immune environment around the tumor and helping immune cells to more effectively recognize and attack cancer cells. This immune response, termed "immunogenic cell death," offers hope as an alternative or adjunctive therapy for skin cancer patients who do not respond well to conventional chemotherapy or radiation therapy. To date, it has garnered attention as an experimental treatment for squamous cell carcinoma and melanoma, with some cases reporting tumor size reduction and decreased recurrence rates.

(4) Psoriasis

Psoriasis is a chronic inflammatory skin disease caused by hyperproliferation of keratinocytes and abnormal immune responses. Cold plasma selectively acts on these hyperproliferative cells, inducing apoptosis and helping to reduce inflammation. Specifically, plasma reduces the expression of proteins such as EGFR and E-cadherin within the skin, regulating cell-cell connections and signal transduction in the affected area.

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Furthermore, it contributes to restoring immune balance by reducing inflammatory cytokines through the anti-inflammatory effects of nitric oxide (NO). It is effective for patients with mild to moderate psoriasis and can also be applied to patients with concerns about the side effects of phototherapy or those requiring combination therapy.

(5) Atopic Dermatitis

Atopic dermatitis is a disease resulting from a complex interplay of skin barrier damage, immune dysfunction, and bacterial infection. Cold plasma helps to improve symptoms by suppressing the growth of Staphylococcus aureus (S. aureus), a bacterium commonly found on the skin, and by alleviating inflammatory responses. Additionally, plasma reduces the secretion of cytokines that cause skin itching (e.g., IL-4, IL-13) and contributes to restoring the skin barrier. Animal studies have observed reduced epidermal thickness and suppression of inflammatory cell infiltration, and some clinical studies have reported a reduction in erythema, itching, and skin dryness. It is particularly useful for patients who need to avoid steroid use or those with recurrent infections.

(6) Chronic Pruritus

Cold plasma contributes to the alleviation of pruritus by blocking the IL-31 pathway, a known major cause of itching. It has also been reported to inhibit peripheral sensory nerve transmission in a manner similar to ultraviolet B (UVB) radiation. Thanks to these effects, symptom improvement can be expected in chronic pruritus unresponsive to conventional treatments, atopic-related itching, and prurigo nodularis.

(7) Other Infectious and Inflammatory Skin Diseases

In addition, cold plasma can be applied to various other skin conditions. It exhibits antibacterial effects not only on bacterial inflammatory diseases such as acne, folliculitis, and impetigo, but also on fungal infections such as onychomycosis and tinea pedis. Furthermore, there are reports that parasites (Leishmania) of tropical infectious diseases such as leishmaniasis are also inactivated by plasma. Rarely, cases of improvement in lesions have been reported in Hailey-Hailey disease, a genetic blistering disorder, suggesting its potential as an adjunctive therapy for rare skin diseases in the future.

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Chapter II.

SYNERJET PRO

Device Introduction

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1. Equipment Overview

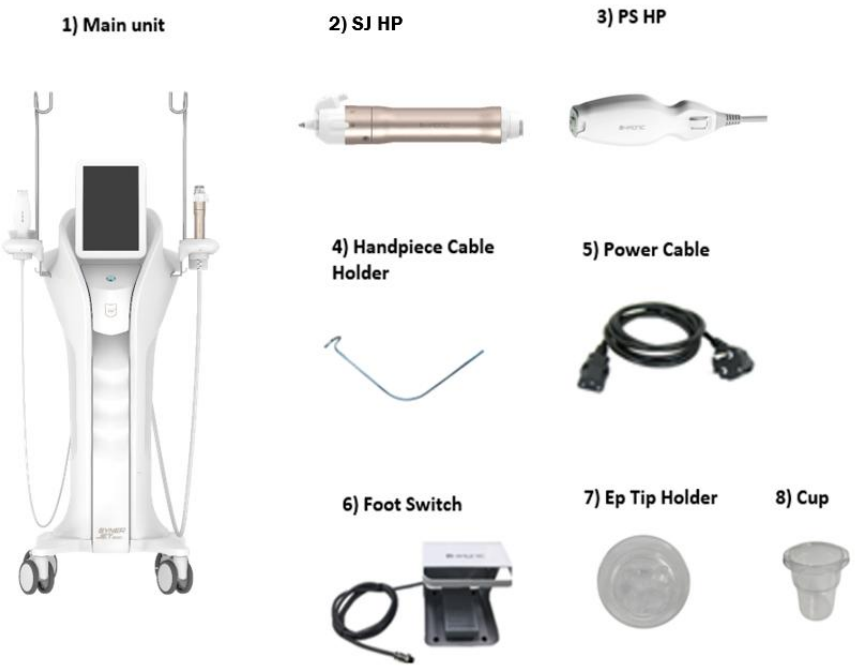
[1] SYNERJET PRO: Maximizing Permeation Synergy of Triple Energies

The SYNERJET PRO is a needle-free injection device developed by Hironic Co., Ltd., a South Korean manufacturer, utilizing a solenoid-driven system. Employing robust jet propulsion, it facilitates the micro-administration of drug (Skin boosters) without the use of needles. Furthermore, it combines Electroporation and Plasma technologies to maximize intradermal delivery and absorption, presenting a total solution system.

[2] Configuration of SYNERJET PRO

The SYNERJET PRO is comprised of the following components:

Number	Components	Q'ty	Remarks
1	Main Body	One	-
2	SJ Handpiece	One	-
3	PS Handpiece	One	Optional
4	Handpiece Cable Holder	Two	-
5	Main Cable	One	-
6	Foot Switch	One	
7	EP Tip Holder	One	-
8	Cup	One	-



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<Basic Configuration of SYNERJET PRO>

Number	Components	Q'ty	Remarks
9	SJ Nozzles – SJN 180, 230	One set	Optional
10	EP Tip - EPT 5, EPT 10, EPT 15	One set	Optional
11	PS Tip	One set	Optional
12	PS Brush Tip	One set	Optional
13	User's Manual	One	-

9) SJ Nozzle

10) EP Tip

11) PS Tip

12) PS Brush Tip

13) User Manual

<Additional Configuration of SYNERJET PRO>

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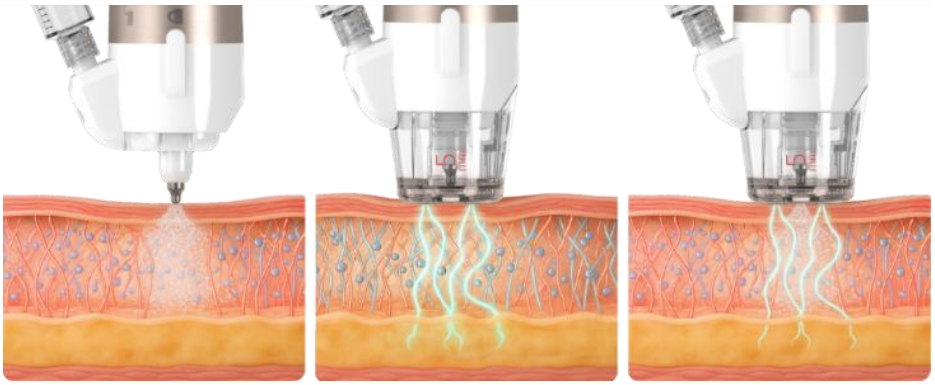
[3] Advantages of SYNERJET PRO

(1) Simultaneous Penetration and Absorption: SJ Handpiece

The SJ Handpiece facilitates rapid and uniform skin booster delivery via microjetting, concurrently enhancing absorption of the administered solution through electroporation. This synergistic combination of mechanisms is designed to optimize absorption efficacy.



(2) High-Performance Nozzle for Rapid and Uniform Delivery

SYNERJET PRO's microjet system allows for precise adjustment of power (P) and injection volume (V), enabling customized parameter settings based on the treatment area, drug type, and skin condition. This allows for precise procedures with controlled depth and dosage.
Furthermore, a repetition rate of up to 25 Hz enables a maximum spray rate of 25 shots per second, significantly reducing treatment time. Internal spray tests have demonstrated stable performance, maintaining a consistent spray pattern and strong injection force at a maximum spray velocity of 580 m/s.

The specially designed cooling nozzle prevents heat generation during spraying, maintaining constant pressure and ensuring stable performance throughout the nozzle's lifespan. The nozzle tip is available in two sizes, 180μm and 230μm, featuring a slender and refined diameter compared to competitor offerings, enabling more precise and subtle injections.

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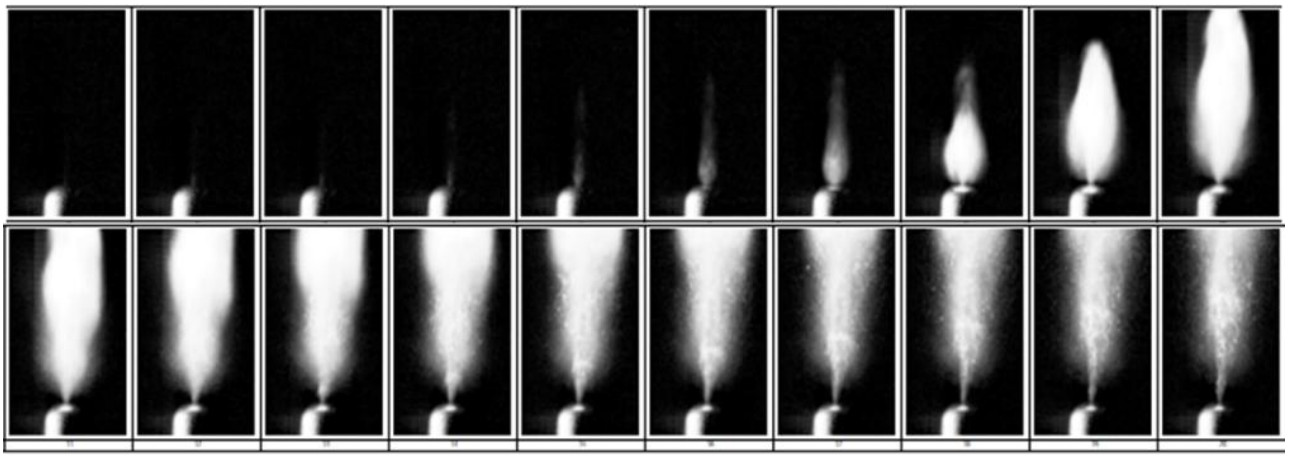

< Self-performing injection speed measurement (2,000,000 FPS) frame interval of 5 μs (microseconds)>

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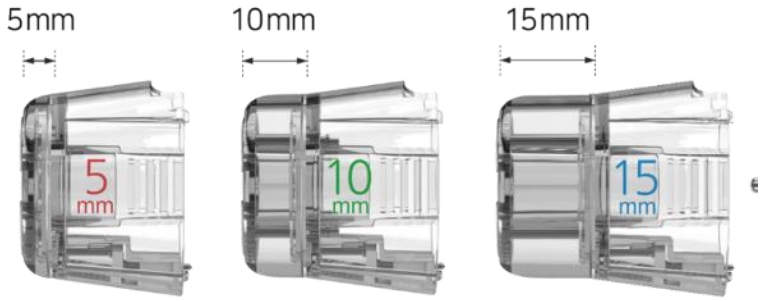
(3) Subcision-Specific Device: Enhanced Efficacy in Scar Treatment

The SYNERJET PRO incorporates a specialized nozzle mold design with a low 33° angle, reflecting the optimal angle for subcision procedures optimized for scar treatment. This design facilitates more precise and optimized treatment angles. Furthermore, the handpiece features a grip ridge ergonomically designed for secure and comfortable handling, enabling improved accuracy and control during procedures.

(4) Enhanced Rejuvenation: 3 Types of Electroporation(EP) Tips

To maximize the efficiency of ampoule absorption, the SYNERJET PRO offers three microcurrent tips (5 mm, 10 mm, and 15 mm) with electroporation technology and distance guides. These tips ensure a consistent separation distance between the nozzle-end and the skin, preventing the splashing of solutions during treatment and ensuring the safety of both the practitioner and the patient.

Moreover, these tips minimize potential drug loss during ampoule delivery and facilitate rapid and deep absorption of the solution into the skin. When delivering ampoules into the dermal layer via a spray method, temporary skin elevation, or an “embossing” effect, may occur. Gentle application of the EP tip to the affected area helps to expedite ampoule absorption and the rapid resolution of this embossing effect.



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(5) FDA-Approved Plasma Technology: PS Handpiece

The SYNERJET PRO incorporates Hironic's FDA-approved plasma technology to provide a synergistic effect for both skin and scalp care. The plasma handpiece aids in eliminating harmful bacteria on the skin surface while simultaneously enhancing the absorption of ampoules. Plasma induces changes in the Skin Membrane Potential, creating an environment conducive to the deep penetration of cosmetic active ingredients. Clinical testing has demonstrated an approximately 4.66-fold increase in skin permeability compared to baseline.

Furthermore, Hironic has developed a specialized plasma brush tip for scalp care, enabling application in hair management and alopecia treatment procedures.

< PS Handpiece: Two tip options available >

(6) Customized Storage for Treatment Areas: 27 Protocol Memory Function

The SYNERJET PRO offers nine memory slots for each of the three treatment areas – face, body, and scalp – providing a total of 27 storable treatment protocols within the device. This function allows users to quickly recall and apply pre-set protocols based on the treatment area and objective, thereby enhancing the consistency and efficiency of the procedure.

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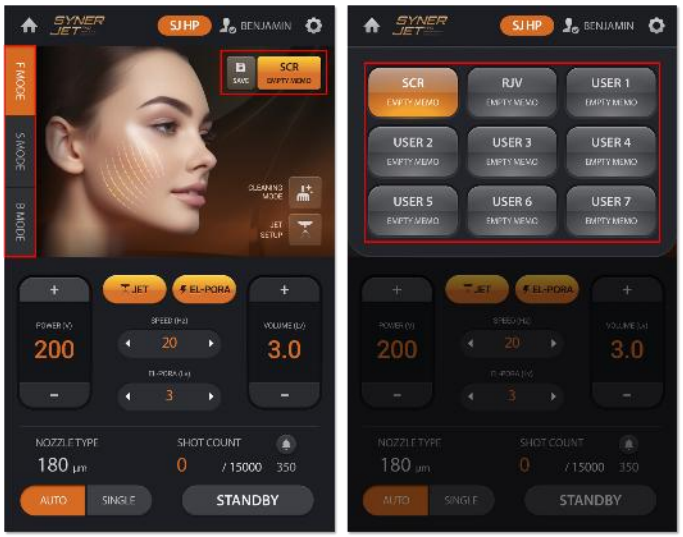
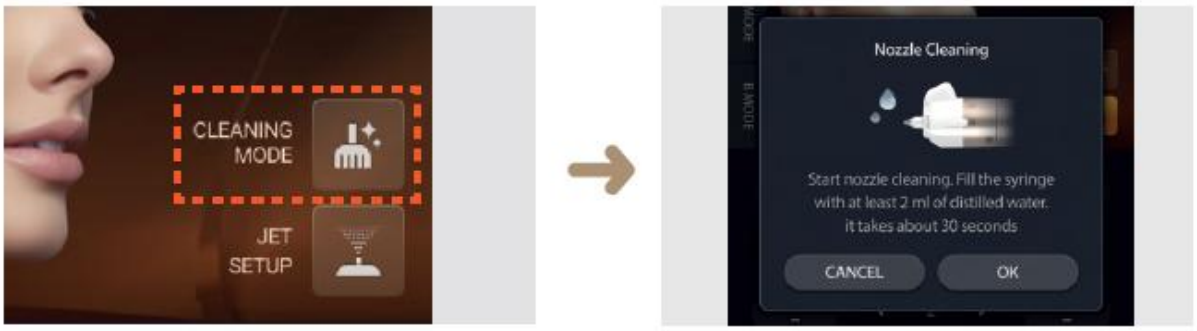


(7) Automated Nozzle Management: Cleaning Mode

The SYNERJET PRO features a nozzle cleaning mode designed to effectively remove residual ampoule components from the nozzle interior following treatment. This mode allows for the automated rinsing of the nozzle interior with distilled water via a one-touch activation, eliminating the need for manual cleaning. Furthermore, a nozzle cleaning cup is provided, enhancing both the convenience and safety of post-treatment hygiene management.



(8) SYNERJET PRO's Efficient Management System

The Treatment Information System (TIS) facilitates remote and convenient management of device usage history and enables expedited customer service. Additionally, the Remote Maintenance System (RMS) automatically records patient-specific parameters, allowing for personalized treatment protocols.

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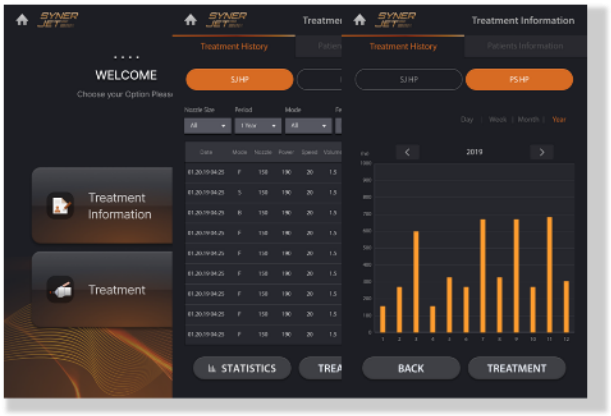
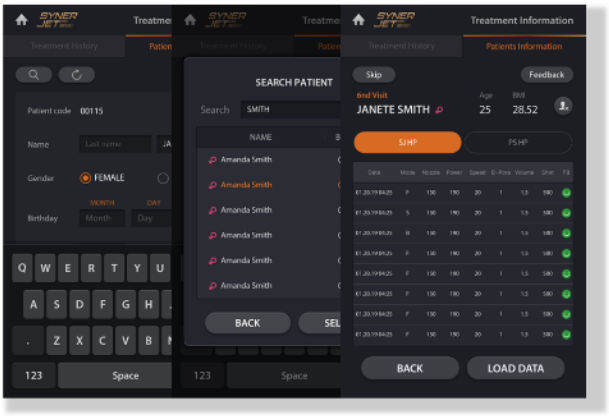


<Treatment Information System (**TIS**)>

Customized treatment facilitated by automatically recorded parameters. Equipped with a parameter logging system for frequently used parameters.



<Remote Maintenance System (**RMS**)>

Facilitating remote management of equipment usage records, Enabling streamlined software and hardware upgrades and expedited pos-sales service.

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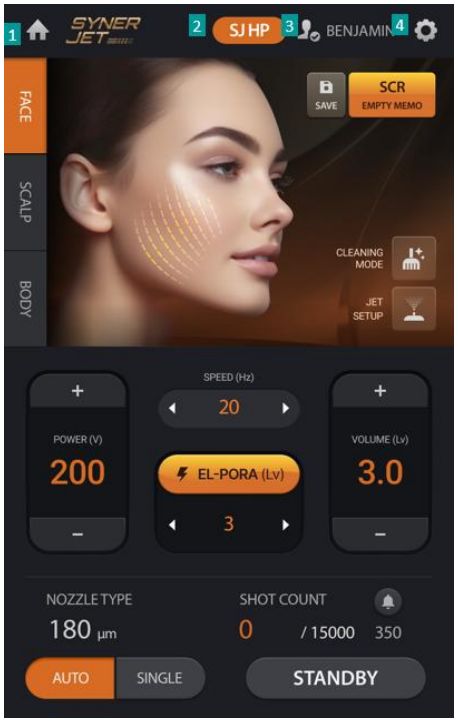
2. Operational Guidelines

[1] SJ Handpiece Procedure

Upon selecting the procedure screen, the connected handpiece will be displayed on the GUI.



[SJ Handpiece Main Screen]

Number	Item	Description
1		Go to the screen where you can select the handpiece.
2	**SJ HP**	The mode of the handpiece is displayed.
3		This icon is displayed on the screen when the Person Information entry page omits the Person Information entry.
4		Click Settings to go to the Settings page.

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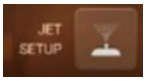
[Procedure Screen]

[Setting Screen]

Number	Item	Description
1	FACE / SCALP / BODY	Mode Settings FACE: Recommended Settings Mode for Face Use SCALP: Recommended setting mode for use on scalp BODY: Recommended setting mode for use on the body (Selecting the mode changes the body image.)
2	POWER (V)	Setting Output Values - 100 to 200 V (unit: 10 V)
3	SPEED (Hz)	Set the dispensing speed - 1~20 Hz (1,2,3,5,7,10,12,15,17,20)
4	VOLUME	Injection volume setting - 1.0 ~ 3.0 (unit: 0.1)
5	EL-PORA (Lv)	Setting Output Values - OFF - 1 Lv: 0.95 Vrms - 2 Lv: 1.11 Vrms - 3 Lv: 1.42 Vrms
6		The F/S/B MODE has access to nine memories each. (The disk shape is recorded.)
7		Wash the nozzle. - 60 seconds (Wash with distilled water.)
8		If you change the parameter value in the non-set screen, it automatically transitions to Ready state.

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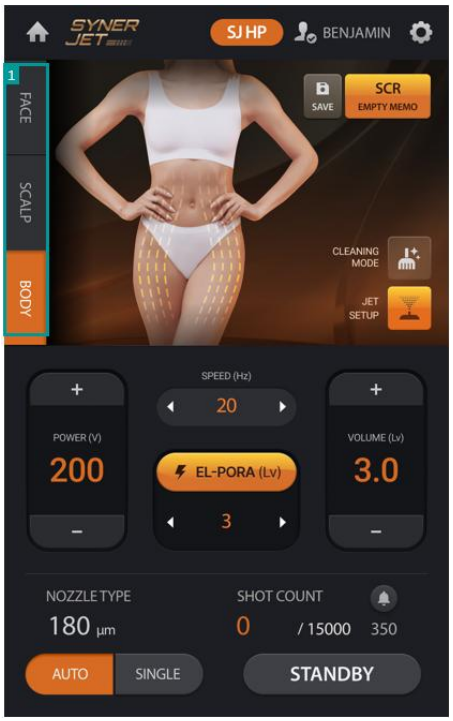
9	AUTO / SINGLE	- Auto: Continuous mode - Single: Single Mode
10	SHOT COUNT	Displays the total number of shots. (Click the alarm button to set the number of shots.)
11	STANDBY	This indicates the standby condition before the shot irradiation. Click 'Standby' to switch to 'Ready'.
	READY	The shot is irradiated by pressing the foot switch in READY(preparing) state.
12	NOZZLE TYPE	The type of nozzle recognized by RFID tag is displayed. - SJN 180: 180 μm

[2] SJ Handpiece Procedure: SCALP/ BODY

[SCALP Procedure Screen]



[BODY Procedure Screen]

Number	Item	Description
1	FACE / SCALP / BODY	Mode Settings FACE: Recommended Settings Mode for Face Use SCALP: Recommended setting mode for use on scalp BODY: Recommended setting mode for use on the body (Selecting the mode changes the body image.)

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[3] SJ Handpiece – Operational Screen

[EL-PORA (ON)]

[EL-PORA (OFF)]

Number	Item	Description
1	Operational Status Screen	The procedure screen is displayed according to the ON/OFF setting of the EL-PORA.

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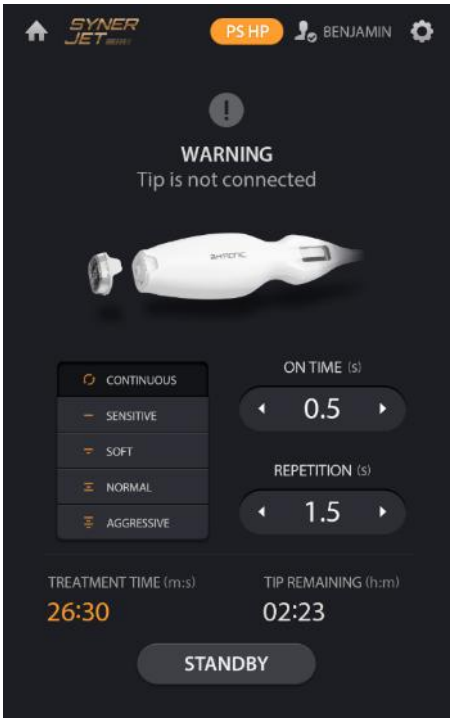
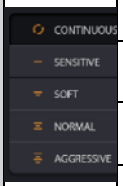
[4] PS Handpiece

[Main screen of the procedure]



[When disconnecting the tip]

Number	Item		Description
1	POWER (Lv)		The power is adjustable from 1 to 5. - 1 Lv : 6 kV - 2 Lv : 7.2 kV - 3 Lv : 8.4 kV - 4 Lv : 9.6 kV - 5 Lv : 10.8 kV
2		CONTINUOUS	Once the settings are applied, the handpiece will continuously generate plasma.
		SENSITIVE	Sensitive skin mode
		SOFT	Soft Skin Mode
		NORMAL	Normal skin mode
		AGGRESSIVE	Rough skin mode
3	ON TIME (s)		Select this menu to adjust the PS operation time. (ON – repeat, SINGLE – repeat once) (0.5 – 5 seconds / interval: 0.5 seconds)
4	REPETITION (s)		Select this menu to adjust the ON Time plasma repeat time. (OFF – No iteration / Single – One iteration) (0.5 – 5 seconds / Interval: 0.5 seconds)
5	TREATMENT TIME (m:s)		Displays the time required for the handpiece (minutes:

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		seconds)
6	TIP REMAINING (h:m)	The remaining time of the tip is displayed (hours: minutes) If the remaining time is marked as 0, the tip shall be replaced with a new one.
7	STANDBY	Click the 'Standby' button to change to the 'READY' button.
	READY	When the procedure is ready, you can step on the footboard switch to release energy.

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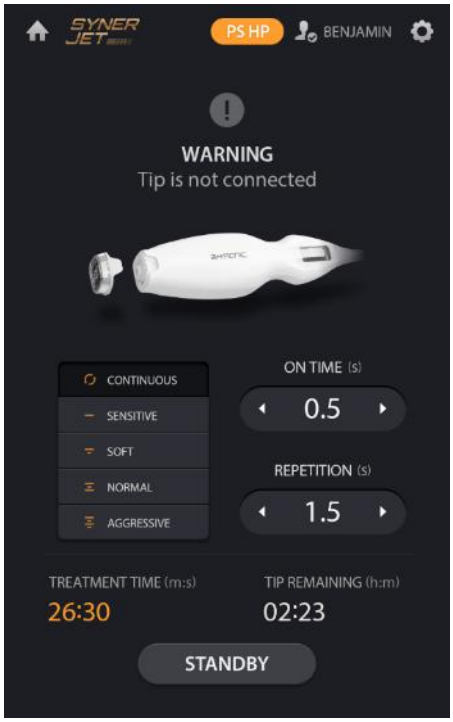
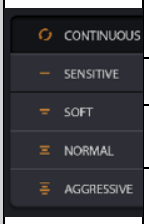
[5] PS Handpiece (PS Brush Tip)

[Main screen of the procedure]



[When disconnecting the tip]

Number	Item		Description
1	POWER (Lv)		The power is adjustable from 1 to 4. - 1 Lv : 5.4 kV - 2 Lv : 5.7 kV - 3 Lv : 5.9 kV - 4 Lv : 6.2 kV
2		CONTINUOUS	Once the settings are applied, the handpiece will continuously generate plasma.
		SENSITIVE	Sensitive skin mode
		SOFT	Soft Skin Mode
		NORMAL	Normal skin mode
		AGGRESSIVE	Rough skin mode
3	ON TIME (s)		rough skin mode
4	REPETITION (s)		Select this menu to adjust the PS operation time. (ON – repeat, SINGLE – repeat once) (0.5 – 5 seconds / interval: 0.5 seconds)

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5	TREATMENT TIME (m:s)	Select this menu to adjust the ON Time plasma repeat time. (OFF – No iteration / Single – One iteration) (0.5 – 5 seconds / Interval: 0.5 seconds)
6	TIP REMAINING (h:m)	Displays the time required for the handpiece (minutes: seconds)
7	STANDBY	The remaining time of the tip is displayed (hours: minutes) If the remaining time is marked as 0, the tip shall be replaced with a new one.
	READY	Click the 'Standby' button to change to the 'READY' button.

[6]

Setting Information

It displays the information of the device.

[Information Menu]

Number	Item	Description
1	HOME	The screen moves to the handpiece selection page.
2	INFORMATION	Displays information.
3	SETTINGS	Displays configuration information.
4	DEVICE S/N	Displays the serial number of the device.
5	SOFTWARE VERSION	Displays the software version.
6	FIRMWARE VERSION	Displays the firmware version.

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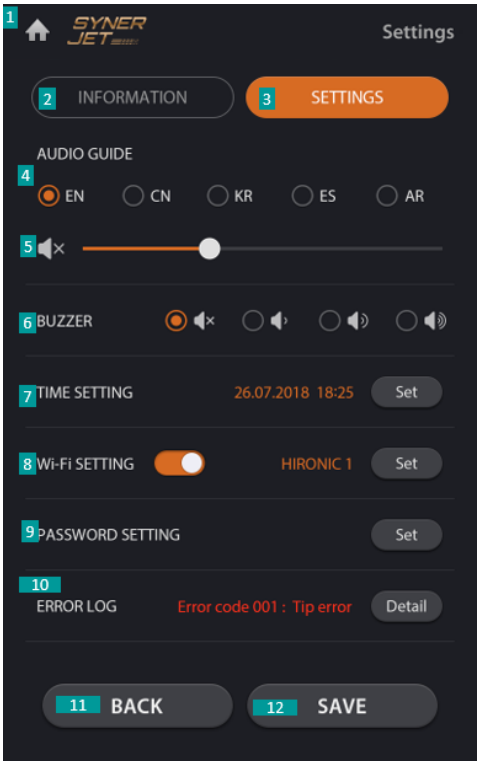
7	COUNTRY CODE	Displays the country code for the device.
8	PS HP TOTAL SHOT	Displays the total number of shots used by the PS handpiece.
9	SJ HP TOTAL SHOT	Displays the total number of shots used by the SJ handpiece.
10	BACK	Return to the previous page.
11	SAVE	Save your settings.

[7] Setting Screen

This screen is used to view device versions, adjust the volume, and configure or review voice prompts.



[Setting Screen]

Number	Item	Description
1		Go to the handpiece selection page.
2	INFORMATION	Displays information.
3	SETTINGS	Displays configuration information.
4	AUDIO GUIDE	Product presentation Speech Language selection (English, Chinese, Korean, Spanish, Arabic).
5		Adjust the volume of the initial message voice language.

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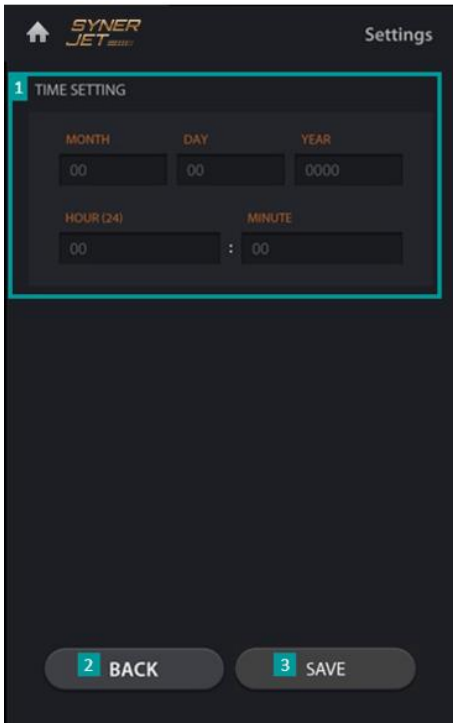
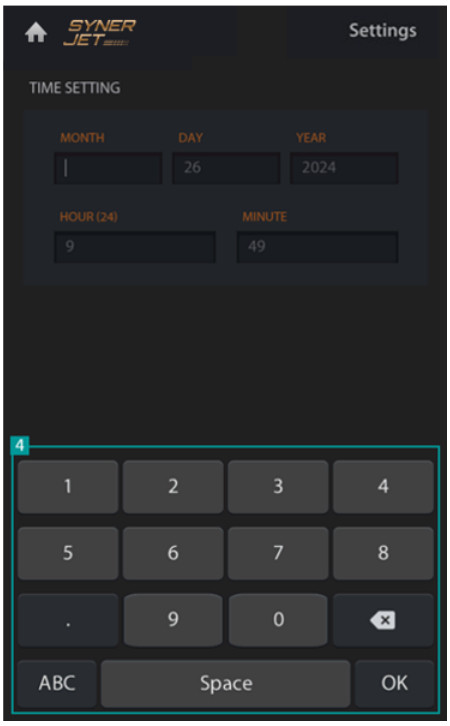
6	BUZZER	Adjust the buzzer volume to four levels (silent, minimum, medium, maximum).	
7	TIME SETTING	Set	7
8	Wi-Fi SETTING	Set	8
9	PASSWORD SETTING	Set	9
10	ERROR LOG	Displays error codes.	
11	BACK	Go to the Treatment Menu screen.	
12	SAVE	This menu is for storing modified information.	

[8] Time Setting

It sets the device's time.



[Time Setting Screen]



[Key Pad]

Number	Item	Description
1	TIME SETTING	Sets the device time.
2	BACK	Return to the previous page.

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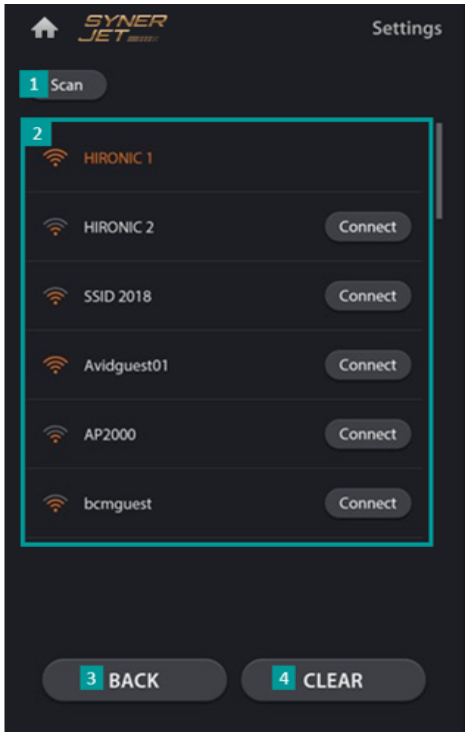
3	SAVE	Save your settings.
4	KEY PAD	Used to select the number to enter.

[9] Wi-Fi Setting Screen



[Wi-Fi Connecting Screen]

Number	Item	Description
1	Scan	Search for accessible Wi-Fi signals.
2	Connect	Connect to the selected Wi-Fi signal.
3	BACK	Go to the main screen of the procedure.
4	CLEAR	This menu is used to reset information.

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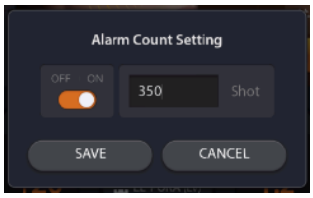
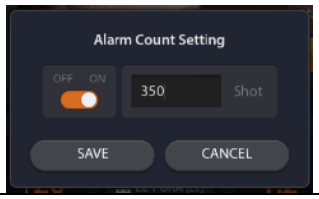
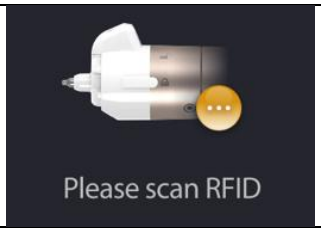
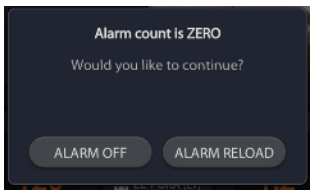
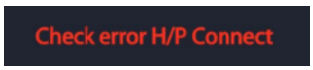
[10] Pop-up Message

Symbol	Description
	  This message appears when you click the alarm button. ※ When you select the desired number of shots and save the settings, the alarm is set. ※ You can turn the alarm on or off.
	**"Please scan RFID"** After clicking on the SJ handpiece, it appears when RFID tag scanning is required. ※ Please scan the nozzle on the RFID tag of the body.
	**"Alarm count is ZERO"** This message appears when the maximum shot counter is reached. Replace the nozzle or tip with a new one. If the memory of the nozzle or tip is deformed (if the number of shots used has changed)
	**"WARNING – Foot Switch is not connected"** This message appears when the foot switch is not connected. Connect the foot switch.
	**"Check error H/P Connect"** This message appears when the handpiece is not connected. Please connect the SJ handpiece or PS handpiece.
	**"Nozzle Cleaning – Start nozzle cleaning. Fill the syringe with at least 2 ml of distilled water. It takes about 30 seconds"** This message appears when the 'Nozzle Cleaning' icon is clicked. If no nozzle cleaning is required, click the 'Cancel' button. If nozzle cleaning is required, fill the syringe with at least 2ml distilled water and click the 'OK' button.

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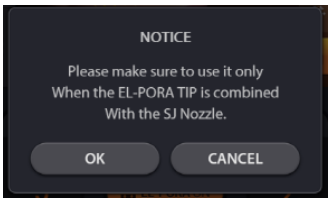
	**"Nozzle Cleaning-Remaining nozzle cleaning time"** This message appears when you click the 'OK' button to start cleaning the nozzle. The message displays the cleaning time (End time: 30 seconds). • If no nozzle cleaning is required, click the 'Cancel' button.
	**"Please make sure to use it only when the EL-PORA TIP is combined with the SJ Nozzle."** After RFID authentication, the following pop-up screen is displayed for 3 seconds: It should only be used with the EL-PORATIP coupled to the SJ nozzle.

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3. Introduction of Handpiece and Constituents

[1] Handpiece Connector

Number	Item Name	Description
1	SJ H/P Connector	The connector of the SJ H/P.
2	PS H/P Connector	The connector of the PS H/P.

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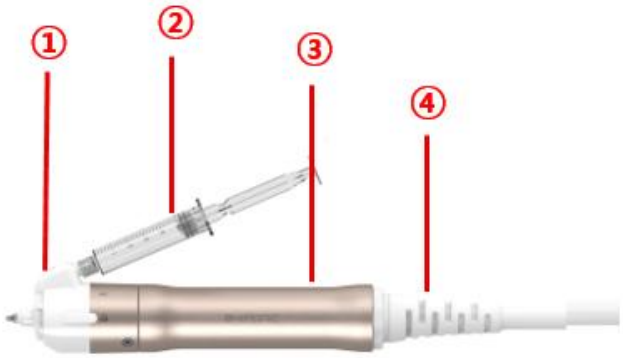
[2] SJ Handpiece (SJ H/P)



H/P LOGO

H/P Socket

Number	Item Name	Description
1	SJ Nozzle Connection	Connect the handpiece to the SJ nozzle.
2	Syringe	It contains a solution that goes into the nozzle.
3	Handpiece Handle	This is the part you hold in your hand during the procedure.
4	Cable	A cable that connects to the handpiece connection at the back of the body.

※ The SJ handpiece should be used with the SJ nozzle.

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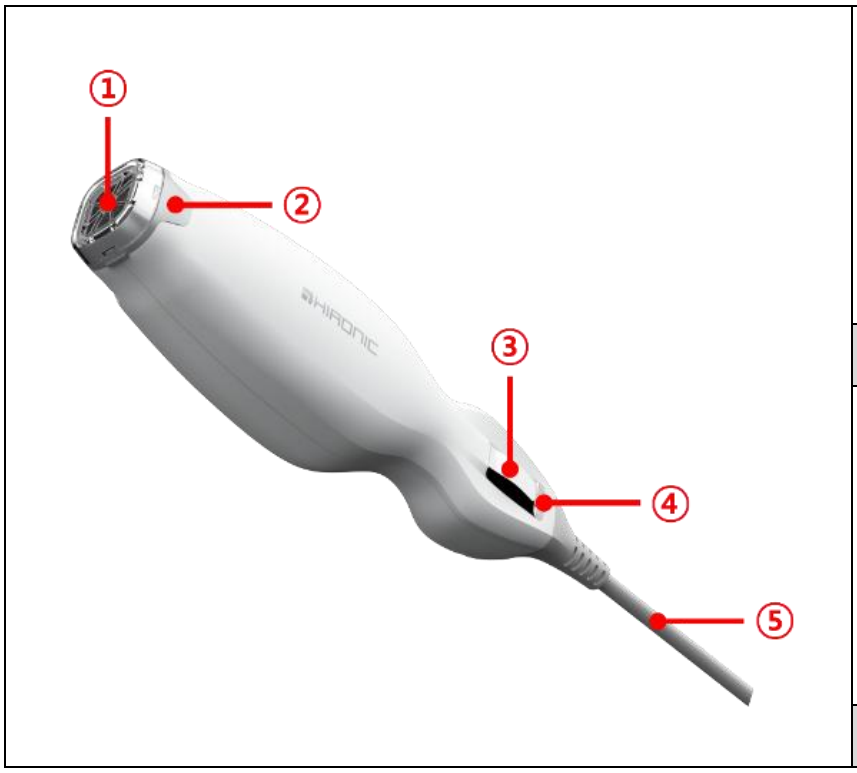
[3] PS Handpiece (PS H/P)



H/P LOGO

H/P Socket

Number	Item Name	Description
1	PS Tip Connections	Connect the handpiece to the PS tip.
2	Handpiece Handle	Use as a handle during the procedure.
3	Hand Switch	Controls the output.
4	Status Indication LED	Displays the operational status of the handpiece.
5	Cable	A cable that connects to the handpiece terminal at the back of the body.

※ The PS handpiece should be used with the PS tip (or PS brush tip).

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[4] SJ Nozzle (SJN)

Number	Item Name	Description
1	Injection part	It's the exit where the drug is sprayed.
2	Syringe Connection	Fastening part connecting Luer-lock syringe.
3	Handpiece Connection	Connect the nozzle and handpiece.

[5] EP Tip (EPT 5, EPT 10, EPT 15)

Number	Item Name	Description
1	EP Irradiation Part	The part where the current is irradiated.
2	Handpiece Connection	Connect the tip to the nozzle.

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[6] PS Tip

Number	Item Name	Description
1	PS Tip Protection Cap	It is a device used to prevent damage to the tip.
2	Irradiation Part	This is the part where plasma energy is emitted.
3	Handpiece Connector	Connect the tip to the handpiece.

[7] PS Brush Tip

Number	Item Name	Description
1	PS Investigation Part	This is the part where plasma energy is emitted.
2	Handpiece Connection	Connect the tip to the handpiece.

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[8] Handpiece Cable Holder

Number	Item Name	Description
1	Handpiece Cable Holder	A holder that holds the handpiece cable.

[9] Foot Switch

Number	Item Name	Description
1	External Cover	This cover/guide prevents the foot switch from being pressed when it falls.
2	Foot Switch	When this switch is pressed, an energy irradiation occurs.
3	Connecting Cable	The cable delivers the foot switch signal to the body.
4	Foot Switch Connector	The connector is connected to the foot switch port at the bottom of the back of the system.

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[10] Power Cable

Number	Item Name	Description
1	Power Cable	A cable that supplies external power to the body. (It is connected to the port at the bottom of the back of the body.)

[11] Cup

Number	Item Name	Description
1	Cup	It is a multi-purpose container.

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[12] EP Tip Holder

EP Tip Holder

Picture combined a handpiece holder

Number	Item Name	Description
1	EP Tip Holder	A holder that holds the EP tip.

[13] User's Manual

Number	Item Name	Description
1	User Manual	A user manual provided.

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[14] Operating Software (Software)

Number	Item Name	Description
1	Operating Software	This software is used to configure/manipulate features and query system status and settings.

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4. SYNERJET PRO's 3 Treatment Modes

The SYNERJET PRO offers three distinct treatment modes, selectable based on the patient's skin condition and intended drug delivery objectives. Each mode is specifically designed to optimize drug delivery to particular skin layers and address specific lesion characteristics, thereby maximizing treatment efficacy and safety. Clinicians can select the most appropriate mode based on the treatment goals and patient condition; these can also be combined to create comprehensive therapeutic strategies.

[1] Jetting Treatment: Intradermal Delivery of Precise Volume via Ultra-fast Micro-Jets

Jetting, the fundamental drug delivery mechanism of the SYNERJET PRO, employs high-pressure micro-jets to rapidly and uniformly deliver active ingredients to the epidermis and mid-dermis. The operator can adjust the power of pressure, enabling precise control over the depth of drug penetration and the delivered dosage. Characteristically, this mechanical spraying method avoids thermal damage, is minimally invasive due to the absence of needles, and minimizes the potential for pain and tissue trauma.

[2] Jet Subcision Treatment: Scar Improvement and Volume Restoration through Fibrous Band Separation

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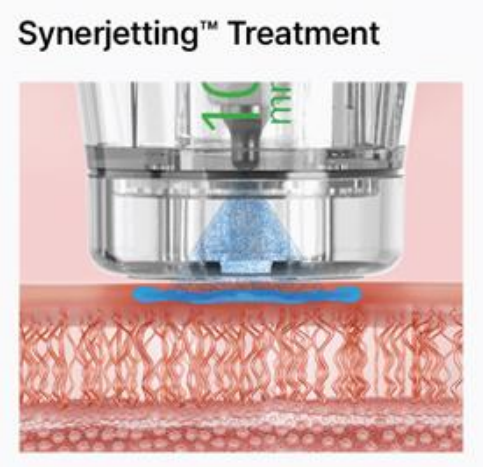
Jet Subcision is a treatment that breaks the scar tissue that is pulling the skin down through jet pressure while injecting active drug ingredients into the area to bring up the scar. Unlike conventional surgical subcision that cut fiber bands by inserting a needle (NOKOR), SYNERJET PRO's jet subscision has the advantage of minimally invasive inducing the same effect while reducing side effects such as pain, bleeding, and bruises.

The specially designed nozzle is optimized for this fine subscision angle setting and is designed to allow sprayed drugs to simultaneously perform physical fiber band separation and component transfer within the tissue.

[3] Synerjetting™ Treatment: Enhanced Absorption via Electroporation



Synerjetting™ is a combined therapeutic approach integrating conventional jetting technology with electroporation. Electroporation temporarily increases cell membrane permeability by altering the skin's surface membrane potential, thereby facilitating the penetration of high molecular weight active ingredients. This functionality is achieved via the SYNERJET PRO's dedicated EP tip, which, when applied to the skin in a massage-like motion, enhances the penetration depth of the sprayed drug.

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Chapter IV.

Q & A

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1. SJ Handpiece

Q1. What is the mechanism by which the SYNERJET PRO delivers the drug?

The SYNERJET PRO employs a needle-free drug delivery system that utilizes high-speed micro-jets to administer drug into the skin. This system propels drug in a jet stream, allowing it to penetrate the epidermis and dermis without the use of needles. The pressure generated by a piston drive forces the liquid within the drug chamber at high velocity through micro-nozzles with diameters of 180μm and 230μm, resulting in ejection speeds of 100–580 m/s.

Q2. Does the drug actually reach the dermis layer, even though it is a needle-free method?

By adjusting parameters such as ejection pressure, nozzle diameter, and speed, penetration depths ranging from the upper to mid-dermis (0.05–2.5 mm) can be achieved.

Q3. What is the level of pain associated with the procedure, and is anesthesia required?

Pain sensitivity varies among patients, leading to individual differences. However, pain level assessments indicate that this procedure often elicits less pain compared to traditional needle-based methods. Anesthesia is not always necessary; however, a topical anesthetic may be applied for approximately 20–30 minutes in some sensitive patients. This decision is contingent upon the practitioner's judgment and the patient's response.

Q4. What is the injection volume per shot, and is it adjustable?

The injection volume can be adjusted based on the treatment interval and pressure settings. The volume per ejection varies depending on the power, volume, and speed set by the practitioner. The approximate injection volume can be adjusted within the range of 0.004 ml to 0.017 ml.

Q5. What causes the formation of blebs (embossing) after treatment?

The blebs are a result of the temporary increase in volume caused by the high-pressure injection of medication into the dermal layer. This embossing is a natural consequence of the penetration process and can be rapidly absorbed and resolved by massaging the area with the EP tip.

Q6. Are the nozzles disposable, or can they be sterilized and reused?

The nozzles are designed for single-use only. To ensure patient safety and hygiene, they shall be discarded immediately after treatment and cannot be sterilized for reuse.

Q7. Approximately how many shots are required for full-face rejuvenation?

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Typically, approximately 3,000 shots are used for a 3cc treatment. The number of shots may be increased up to 4,500, depending on skin thickness and facial surface area.

Q8. At what angle should the handpiece be held during scar treatment or rejuvenation procedures?

- Scar Treatment: A low angle (approximately 33 degrees) is recommended to minimize tissue dissection. While existing devices may tilt up to 45 degrees, the SYNERJET PRO enables precise and gentle treatments at 33 degrees due to its specialized nozzle design.
- Rejuvenation: It is recommended to apply the treatment in a toning manner at a perpendicular (90-degree) angle to the skin using the EP tip.

2. EP tip

Q1. What is the function of electroporation?

Electroporation momentarily alters the potential difference across the skin surface, increasing cell membrane permeability. This maximizes the penetration and absorption efficiency of dispensed ampoules into the skin.

Q2. Can the EP mode be used independently?

Yes, the EP mode can be used independently. While it can function like other electroporation devices for localized drug delivery, when used in combination after jet injection, it is more effective in enhancing drug absorption.

Q3. What are the differences between the 5mm, 10mm, and 15mm EP tips?

The varying tip sizes influence the penetration depth based on the distance maintained between the nozzle end and the skin. In general, the 5 mm tip reaches the deepest layer, while larger numbers correspond to shallower, more superficial penetration.

3. PS Handpiece

Q1. Is it better to perform plasma treatment before or after spraying?

Plasma is most effective on dry skin; therefore, it is recommended as a pre-treatment. This allows for sterilization of the skin surface and a plasma channeling effect that enhances absorption by a factor of 4.66.

Q2. Is it effective for hair loss treatment when used on the scalp?

By utilizing a scalp-specific brush tip, medication can be evenly applied. Electrical stimulation can then be used to stimulate blood flow and drug absorption, aiding in the improvement of hair loss.

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4. Treatment

Q1. How should treatment intervals be determined?

While it depends on the ingredients of the medication and the patient's skin condition, repeated treatments at intervals of 2 to 4 weeks are generally appropriate. Consider the skin's regeneration cycle when determining the interval.

Q2. What type of skin booster is suitable for use?

Water-based products with low viscosity are suitable. Highly viscous ampoules or formulations with large particles are not recommended, as they can cause nozzle clogging. If necessary, consider dilution with normal saline (N/S).

Q3. Can it be used on the face, scalp, and body?

The SYNERJET PRO features dedicated settings for the face, scalp, and body. It also has a built-in memory function with 27 storable protocols tailored to each area, enhancing ease of use.

Q4. What are the precautions to take after a SYNERJET PRO treatment?

For 2-3 days after treatment, avoid strong sun exposure, saunas, and strenuous exercise. Hydration is necessary to promote absorption. Mild redness or swelling will subside naturally within a few hours.

Q5. Can SYNERJET PRO be used in combination with radiofrequency (RF), HIFU, or other treatments?

Yes, combination treatments are possible. However, the order and intervals of the treatments should be adjusted at the practitioner's discretion.

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Chapter VI.

Appendix

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1. Precautions

[1] Pre-Procedure Precautions

Prior to undergoing a SYNERJET PRO procedure, the following precautions shall be observed:

- The procedure is not recommended for women who are pregnant or breastfeeding due to the potential for unpredictable skin reactions resulting from hormonal changes.
- The procedure should be avoided in individuals with open wounds, surgical sites, hemorrhagic conditions, or a predisposition to bleeding, as stimulation of the treated area may induce bleeding.
- The use of this device is contraindicated in patients with implanted electronic medical devices such as pacemakers, due to the risk of electrical interference.
- Prior confirmation is necessary to ensure there are no allergies or contraindications to the medications being used. A thorough review of the patient's medical history, current medications, skin condition, and any individual specificities is mandatory.
- Direct or indirect treatment of the ocular region is strictly prohibited. The use of protective eyewear is mandatory during the procedure.
- The procedure should be immediately discontinued if symptoms such as pain, adverse reactions, edema, or rash occur during the procedure. The patient’s condition shall then be carefully monitored.

[2] Post-Procedure Precautions

The following instructions should be provided to the patient and adhered to during the immediate post-procedure period and throughout the recovery process:

- Minor bleeding, pinpoint bruising, redness, or ecchymosis may be observed at the injection site immediately following the procedure. These are common reactions that typically resolve spontaneously within 3 to 7 days.

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- The application of regenerative creams and moisturizers is recommended during the recovery period, and the consistent use of sunscreen is mandatory. Light makeup is permissible, but the use of irritating or harsh cosmetics should be avoided
- For a minimum of 2–3 days post-procedure, physical stimulation of the treated area, such as vigorous massage, should be avoided. Excessive stimulation may trigger inflammatory responses, bruising, or pain.
- For approximately 7 days post-procedure, saunas, steam rooms, prolonged exposure to heat, and alcohol consumption should be avoided, as these may cause vasodilation or delay the recovery process.
- Strenuous exercise that induces excessive sweating may interfere with skin recovery and medication absorption; therefore, it is advisable to avoid such activities for at least 2–3 days.

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2. Patient Consent (Form)

Patient Name		Birthdate	
Current Medication		Name of the Medicine	
Presence or Absence of Allergies		Allergic Name	
Past Medical History		Disease	
Presence or Absence of Past Procedures		Name of Treatment	

▶ If you have a skin condition in the area where you wish to receive the procedure, the procedure can be performed after recovery.

▶ The procedure is restricted in the following cases:

- Pregnancy or breastfeeding
- Open wounds, surgical sites, bleeding disorders, or potential for bleeding
- Implanted electronic medical devices such as pacemakers
- Allergic reaction to the medications used

This procedure can be applied for various purposes, including skin hydration, elasticity improvement, pigmentation reduction, scar improvement, and scalp and hair loss care. Repeated treatments at regular intervals may be recommended to optimize the results of the procedure. Even if the procedure is performed normally, please be aware that the following common reactions may occur temporarily:

Erythema (redness), Swelling (swelling)	Possible treatment site immediately after treatment, usually resolved within hours after treatment
Pain	You may experience instantaneous discomfort during the procedure and after the procedure, contact may cause discomfort and tenderness
Bruise	Mild bruises caused by vascular damage to soft tissue can occur infrequently, Usually, resolution within a few days of treatment

Although significant improvement is observed in most procedures, the degree of improvement may be perceived as insignificant in some patients due to differences in skin condition. Appropriate application of the treatment program provided by the clinician is necessary to achieve optimal results.

Refunds are not possible for any reason after the procedure is completed. This also applies to package deals, even if partially used.

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I have read and understood the above consent form prior to the procedure and acknowledge and agree to the expected results and management methods of the procedure.

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Please do not hesitate to contact us should you have any inquiries.

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Specifications

Convenience system	RFID, TIS, RMS, Cleaning mode , Jet set-up mode	
Consumables	Nozzle tip, ELPORA tip, PS tip, Brush tip	
Nozzle	Diameter	180μm, 230μm
	Shots	9,000
EL-PORA tip	Distance control	5mm, 10mm, 15mm
Energy generation method	Solenoid	
Energy source	Microjet, Electroporation, Plasma	
LCD screen	12.1"	
Power consumption	700VA	
Dimensions	510(W) x 530(L) x 1,200(H) mm	
Weight	43KG	
EL-PORA Handpiece	Jet speed	150-500m/s
	Injection pressure	100 bar (101.971621kgf/㎠)
	Injection speed	1-25Hz
	EP intensity	1-4Lv
PLASMA Handpiece	Power Level (Lv1~5) + Brush tip Level (Lv1~4)	

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