Received: 4 August 2020 | Accepted: 10 August 2020

DOI: 10.1111/jocd.13674

REVIEW ARTICLE

JCD Journal of Cosmetic Dermatology WILEY

Biochemical and physical actions of hyaluronic acid delivered by intradermal jet injection route

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Abstract

Background: Administration of exogenous hyaluronic acid (HA) by liquid jet injection is considered as a beneficial therapy for dermatologic conditions.

Aim and methods: The paper reviews variety of factors enhancing efficacy and safety of hyaluronic acid implemented for the intradermal jet-injection treatment modality.

Results: Kinetic energy of the pneumatically accelerated jet activates two parallel mechanisms of action—mechanical and biological—which act synergistically to initiate and augment the regenerative effect in skin. Jet-induced micro-trauma stimulates collagen synthesis and tissue repair without inflammation and significant damage to the tissue and blood vessels. Aside from the biophysical stimulation of dermal fibroblast, the biomolecular properties of exogenous HA provide excellent clinical results for skin atrophy, remodeling of dermal scarring, and reverse formation of fibrotic tissue. The effect is mediated by HA-specific cell receptors and depends on molecular weight and the rheological properties of HA polymer. Skin mechanical properties play a key role in predicting HA dispersion patterns. Tolerability and safety of the treatment approach are determined by the jet's physical impact on the tissue and/or by the safety profile of the injected material.

Conclusion: Although pneumatic jet delivery of a hyaluronic acid has a limited use in clinical practice, this treatment approach has a strong potential for extended implementation in aesthetic dermatology. The synergistic mechanism has significant advantages of predictable and rapid clinical outcomes with a low discomfort. Additional well-designed investigations are required for establishing a scientific foundation and guidelines for this treatment modality.

KEYWORDS

acne scars, AirGent, EnerJet, hyaluronic acid, hypertrophic scars, liquid jet injections, needle-free injection, pneumatic jet

1 | INTRODUCTION

An intradermal administration of hyaluronic acid (also known as hyaluronan) is currently a primary mean for skin regeneration. Besides viscoelastic and filling effect, hyaluronic acid (HA) enhances structural integrity of extracellular skin matrix (ECM) and provides tissue repair through interactions with cell surface receptors.[1] Alternative to traditional needle injections, jet delivery of HA is needle-free and less dependent on the injector's skills and experience, therefore associated with much lower rate of adverse events. This paper reviews the factors optimizing clinical outputs of HA treatment administered by jet injection.

2 | PRINCIPLE OF LIQUID JET INJECTION

In medicine, a liquid jet is a stream of fluid forcefully ejected by various types of pressure-driven mechanisms. Traditional spring-loaded jet injectors, such as Dermojet (AKRA, France), act at the fixed pressure, predetermined by the spring size. Pneumatic jet devices (eg, EnerJet or AirGent by PerfAction Technologies, Israel) are powered by air compressor which allows for a wide range of pressure and more predictable distribution of the injected material in the tissues.[2] The high velocity of the jet stream (up to 150 m/s) together with its small 200-μm diameter allows for a quick penetration of the skin, with minimal or no pain. The impact transforms the jet into a "storm" of tiny micro-droplets (10-100 μm in diameter) advancing radially until their kinetic energy is exhausted (Figures 1 and 2). As deposited material increases the skin volume, it bulges into temporary papule, lasting from a few hours to days depending on the nature of the injected HA (Figure 3).

3 | BIOMOLECULAR EFFECT OF JET-INJECTED HA

Jet-induced delivery of HA is thought to activate two synergistic mechanisms, related to biological action of HA and to the stimulating effect of the liquid jet. Physical tension applied by the micro-droplets on the surrounding extracellular matrix (ECM) causes micro-injury to the encountered collagen fibers and subsequently initiates a healing mechanism without excessive scarring. HA was shown to reduce presence of the senescent mesenchymal cells normally associated with the scar-producing wound healing.[3] Exogenous HA augments the repair by inducing fibroblast migration and enabling their differentiation to myofibroblasts.

Wang[4] postulated a cause-effect link between production of type I collagen and morphological stretching of fibroblasts following injection of exogenous cross-linked HA. Meran[1] with in-vitro evidence proposed that HA molecules bind to CD44 cell receptors on fibroblasts and promote new collagen production, together with other positive effects. Turlier[5] demonstrated increase in procollagen following mechanical stretching of ECM in dermal injections of HA. Kwon[6] related collagen-stimulating effect of pneumatically injection HA to the activation of vimentin, cytoskeletal protein responsible for maintaining cell integrity in wound healing.

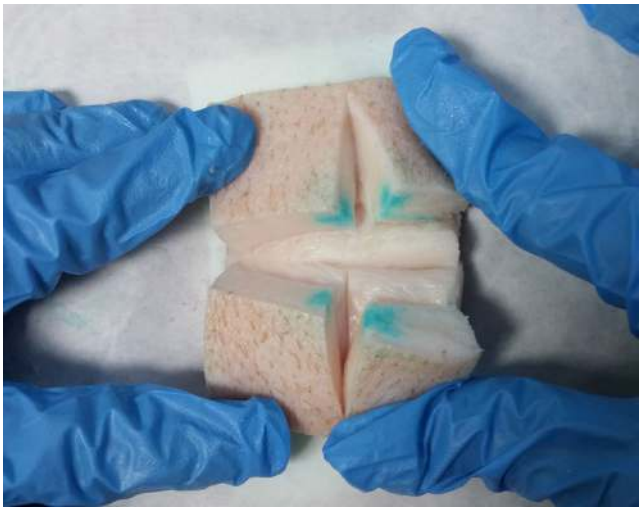

FIGURE 2 Gross anatomy of liquid jet injection (porcine skin). Sections performed at the entry point demonstrate a multiplanar dispersion of the injected contrast (green ink) (Courtesy of PerfAction Technologies)

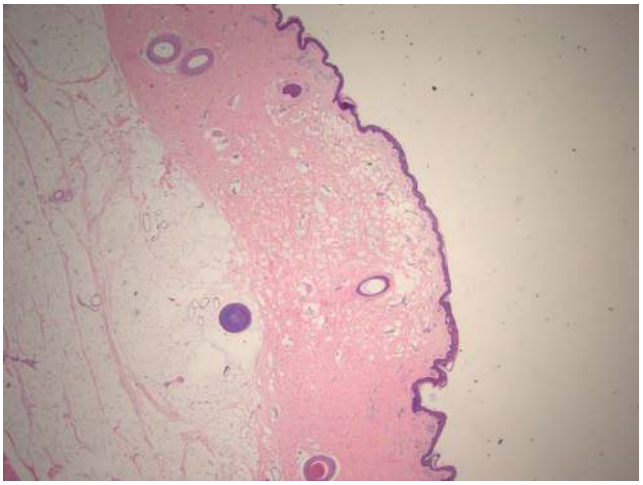

FIGURE 1 Histological appearance of HA deposition after jet injection (porcine skin): wide dispersion of HA micro-droplets (multiple spaces) is extended through the whole dermis. Epidermis appears intact (×1.25 HE staining) (Courtesy of PerfAction Technologies)

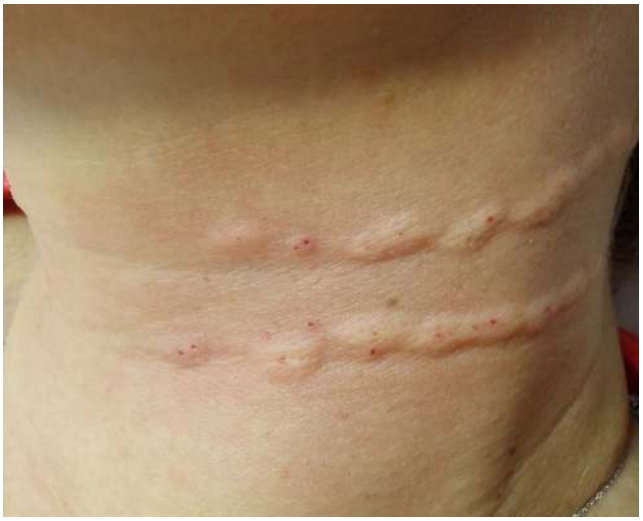

FIGURE 3 Treatment of neck rhytidosis with jet-injected HA: appearance of transient dermal papules indicates penetration and intradermal dispersion of the material (Courtesy of PerfAction Technologies)

TABLE 1 Biologic activities of hyaluronic acid in relations to the molecular weight and interaction with HA-specific cell receptors (based on Litwiniuk *et al* 2016[16])

Molecular size	CD44	RHAMM	TLR	Inflammatory response	Angiogenesis	Anti-oxidative properties
High molecular weight HA	Prevention of cell apoptosis, stimulation of CD44 clustering and signaling	Induction of inflammatory response: stimulation of fibroblast proliferation and migration	Suppression of inflammatory cascade in acute injury	Anti-inflammatory effect: diminished recruitment of inflammatory cells and decelerated migration of stem cells	Anti-angiogenic response: inhibition of endothelial cell proliferation, motility, and sprout formation	Reduced oxidative stress, diminishes cell apoptosis
Low molecular weight HA	Disruption of CD44 clustering and inhibition of kinases activation		Activated production of pro-inflammatory cytokines and stimulation of lymphocytes	Pro-inflammatory effect: stimulated production of pro-inflammatory cytokines, chemokines and growth factors	Pro-angiogenic response: stimulation of vascular endothelial cells proliferation, migration, and tubule formation	Inhibited free radicals for the antioxidant and protective effect

Abbreviations: RHAMM, Receptors for Hyaluronan-Mediated Motility receptors; TLR, Toll-Like Receptors.

We believe that the jet-induced neocollagenesis differs from the inflammatory-stimulated collagen regeneration associated with energy-based devices. The accelerated dispersion of HA micro-droplets causes microscopic tears in the dermal matrix at the level below the threshold that triggers a clinically detectable inflammatory response. The mechanism is believed to be similar to the noninflammatory healing naturally occurring in other mesenchymal tissues, such as a proliferative healing of the micro-injury in tendons resulted from an acute physical overload.[7]

Although pneumatic ejection applies much higher pressure on HA than in needle injection, the mechanical strain does not diminish its biological activity. The mechanism is modulated through HA binding to HA-specific cell receptors (CD44, TLR, and RHAMM) and leads to achieving the molecular weight-dependent biological response.[8] Although the quantitative definition of high and low molecular weight still varies between researchers, yet many consider HA with low molecular weight (LMW-HA) as pro-inflammatory and angiogenesis-stimulating, whereas HA with high molecular weight (HMW-HA) displays anti-inflammatory, immunosuppressive, and anti-angiogenic effects[9-11] (Table 1). Through interaction with CD44, HMW-HA activates the wound healing process and induces cell migration into the wounded area. Additionally, exogenous HMW-HA clusters CD44 receptors to a protective coating which masks their death and prevents apoptosis of the cell.[10] HA mediation of the receptors for hyaluronan-mediated motility (RHAMM) stimulates inflammation and tissue repair by activation of macrophages and fibroblast proliferation.[9] Finally, through regulation of the toll-like receptors (TLRs), HA controls the cellular reaction to pathogens. LMW-HA activates TLRs to the production of pro-inflammatory cytokines and chemokines effectively provoking an inflammatory mechanism. HMW-HA, on the contrary, forms a shield around TLR which protects the cell surface receptors from outside and prevents the cellular inflammatory response.[11]

Nevertheless, for the jet treatment, a subclinical level of inflammation could be desirable and would contribute to the soft tissue regeneration by activating an adjunct physiological pattern, without significantly aggravating postinjection morbidity and downtime. The inflammation comes from degradation of the injected HA polymer, either by intrinsic hyaluronidase or through oxidative de-polymerization induced by reactive oxygen species (ROS).[12] Percent of cross-linking in commercial dermal fillers does not exceed 20% of HA chain,[11] so the unlinked portion is easily degraded and continuously "yields" small HA fragments. The low-weight pro-inflammatory fragments activate macrophages and induce chemokines maintaining a low inflammatory level in the skin all the time.[13]

4 | CUTANEOUS DISTRIBUTION AND RHEOLOGY-RELATED INTEGRATION

Spread of HA increases its availability for the tissue interaction, but the scatter is limited by the skin friction. The area of dispersion was

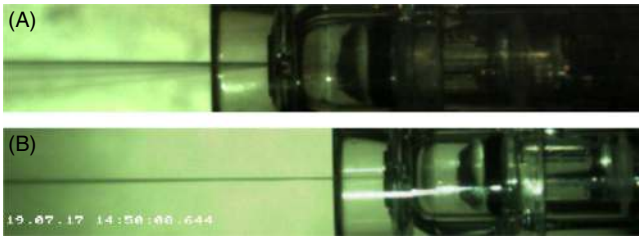

FIGURE 4 High viscosity of injected HA causes premature dispersion of the jet stream (A) and unable skin penetration. HA with low viscosity (B) optimizes penetration by generating a consolidated and focused stream of fluid (Courtesy of PerfAction Technologies)

found to be inversely related to the droplet mass.[14] The lighter particles showed markedly wider and deeper cutaneous propagation in comparison to the limited spread of the heavy droplets.[15]

The multilayered structure and variability in the skin viscoelastic properties further create resistance to the HA dispersion.[15,16] Erlendsson[17] speculated that deposition patterns can be influenced by the porosity, homogeneity, and density of the injected tissues. With the age-limited elasticity of the skin, the jet would need higher force to disperse the droplets.[18] A thorough hydration of the skin prior to injection not only increase cutaneous elasticity and extend HA distribution upon penetration, but also allows achieving it at the lower pressure and with minimal or no discomfort.

Rheological properties (cohesivity and viscosity) additionally control cutaneous integration of injected HA and, otherwise, the clinical outcomes. HA with increased cohesivity decreases resistance of the micro-droplets to spread and, accordingly, extends their availability for bio-integration into surrounding tissues.[19] Viscosity characterizes capability HA to flow and, together with cohesivity, determines its distribution pattern in soft tissue. Majority of commercial dermal fillers are structurally presented as a liquid fraction integrated within a semi-solid insoluble medium (gel).[20] Such design guarantees high viscosity of HA polymer but makes it impossible to be used "as is" for jet injection. In order to create a liquid stream, viscosity of commercial fillers needs to be reduced through simple dilution (Figure 4). La Gatta[20] demonstrated that dilution will affect only the water-soluble fraction of HA hydrogel, leaving the insoluble portion intact.

Modification of the viscosity was shown to decrease friction of HA droplets in the skin and subsequently improve its integration without diminishing the bio-stimulatory effect.[15,21] Low viscosity, especially in combination with high cohesivity, could be attractive in the treatments of the skin atrophy for which "good spreading ability"[12] of the HA filler is required (Table 2). Alternative in this case can be the administration of noncross-linked HA (NCL-HA). While NCL-HA shows rather modest proliferative effect,[8] its functional and longevity shortage was proven to be substituted by mechanical impact of pneumatic injections.[22,23]

Although it is uncertain how amount of HA delivered to each point influences the treatment outcome, the backflow phenomenon should be taken in consideration. The mechanism is multifactorial and, first of all related to overflow of the penetration, micro-channel which is formed at much slower rate than the rate it is filled.[2] Under elastic stress caused by the material dispersion, the skin rebounds and additionally contributes to the backflow. As viscosity of the jet-injected HA is 4-5 times lower than of the original filler, it further eases unavoidable loss, similar to other low-viscosity injectables,

TABLE 2 Bio-morphological and rheological parameters of hyaluronic acid fillers recommended for jet injection cutaneous treatments

Indications	Molecular weight	Cross-linking	Cohesivity	G′
Skin atrophy	LMW + HMW	CL or NCL	High	Low
Elastosis	HMW	CL	High	Low
Stretch marks (*striae alba*)	LMW	CL or NCL	High	Low
Atrophic acne scars	N/A	Biphasic CL	Low	High
Post-traumatic depressed scars	N/A	Biphasic CL	Low	High
Hypertrophic scars	HMW	CL	High	Low
Keloid scars	HMW	CL	High	Low
Skin laxity, severe	LMW	Biphasic CL	High	Low
Skin laxity, mild	HMW	CL	High	Low
Nonsurgical skin lift, face	HMW	Biphasic CL	High	Low
Nonsurgical skin lift, neck	HMW	Biphasic CL	Highest possible	Lowest possible
Décolleté rejuvenation	HMW	NCL	Highest possible	Lowest possible

Abbreviations: CL, cross-linked; HMW, high molecular weight; LMW, low molecular weight; NCL, noncross-linked.

such as botulinum toxin. Backflow can be responsible for up to 15% loss of injected material[24] and may contribute to inconsistency in the treatment outcomes.

5 | CLINICAL EFFECTS

Comparing to the volumizing effect of manually injected HA, jet injections boost structural regeneration of the skin. The triggered injury-healing process promotes the neocollagenesis which is thought to gradually replace the initial HA hydration effect.[25] Progressive reduction of rhytidosis and improved turgor and elasticity[26-28] can be observed as a new collagen continues to be accumulated for approximately 3-6 months after the treatment[29] (Figure 5). Under higher injection pressure, HA micro-droplets can be dispersed into deeper layers and generates a volume-generated tension on fibro-septal system (retinacula cutis) and superficial musculo-aponeurotic system. Achieved results demonstrated tightening and lifting of the sagging facial skin.[22,30]

In the treatment of acne scars, the jet is injected directly into the scar depression in the manner comparable to manual surgical subcision, but without typical swelling, bruising, and pain. HA functions as the media which not only deliver forces on the scar but also bio-modifies it. Pressurized spread of HA droplets creates microscopic channels through the scar and loosens its adhesion to the underlying tissue. Under repetitive injections, the scar is released and gradually rises to the level of the surrounding skin (Figure 6).

Simultaneously, exogenous HA regulates the cellular response to activated growth factors and increased fibroblast migration.[30] Through phenotypic changes in macrophages activity, HA either reverses the inflammation in the evolving acne scars[31] or promotes it at the beneficially low level in old atrophic scars, without aggravating downtime. Postinjection dermal papule provides a temporary filling that gives patients an initial high satisfaction (Figure 7). As this effect subsides due to HA reabsorption, the tissue regeneration starts and corrects the atrophy permanently.

It is recommended to customize administered HA to the scar age and degree of environmental damage (solar elastosis, smoking, etc). For the younger shallow scars surrounded with the undamaged healthy skin, a highly cohesive HA with prevailing regenerative drive would be desirable (Table 2). The old and deep scars will benefit from the enhanced filling by less cohesive and more cross-linked HA. For the scars surrounded by elastotic skin, hybrid HMW/LMW-HA with significant dermal regeneration drive would be indicative.

Clinical efficacy of jet-injected HA was conveyed by achieving a significant improvement in acne scar appearance along with a high degree of patient satisfaction.[32,33] The results were comparable to HA treatment of acne scars by various manual injection techniques.[34,35]

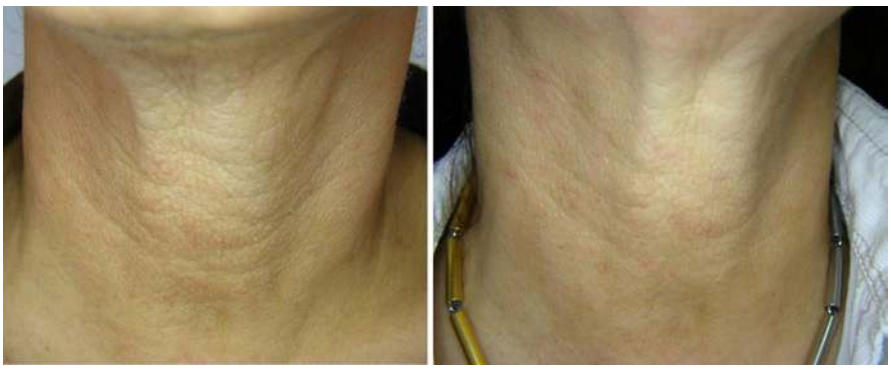

FIGURE 5 Treatment of rhytidosis and skin laxity in neck region with jet-injected HA (Restylane Fynesse, Galderma SA, Switzerland): before and 3 mo after 2 treatments (Courtesy of PerfAction Technologies)

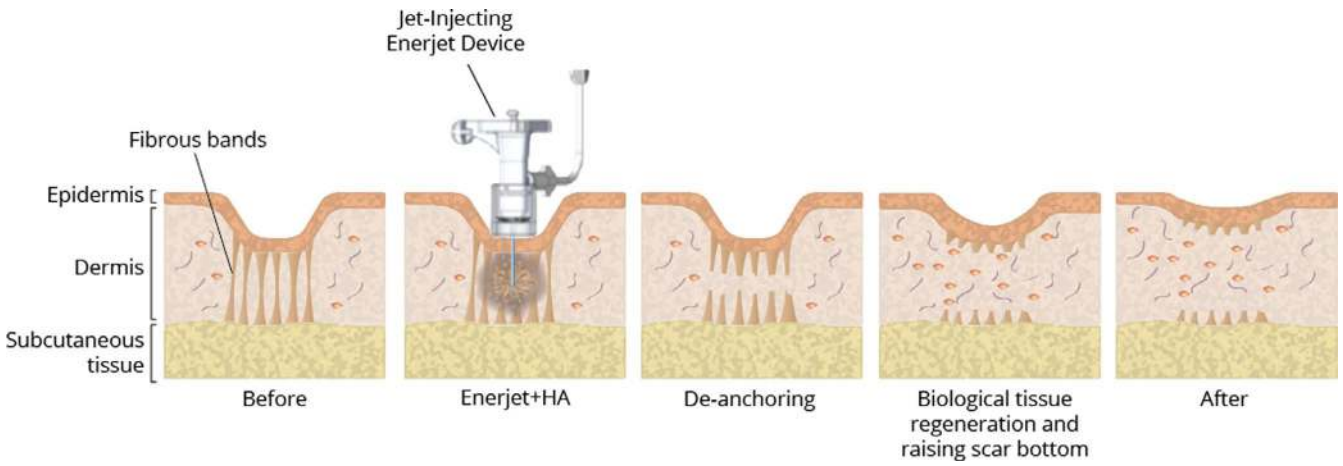

FIGURE 6 Schematic of the liquid subcision mechanism (Courtesy of PerfAction Technologies)

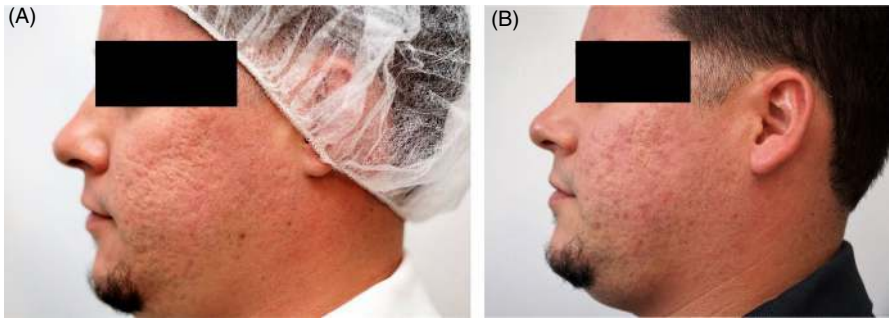

FIGURE 7 Initial filling effect of the jet-injected HA on acne scars: before the treatment (A) and 5 d after the treatment (B) (Courtesy of F-Face clinic, Puerto Rico)

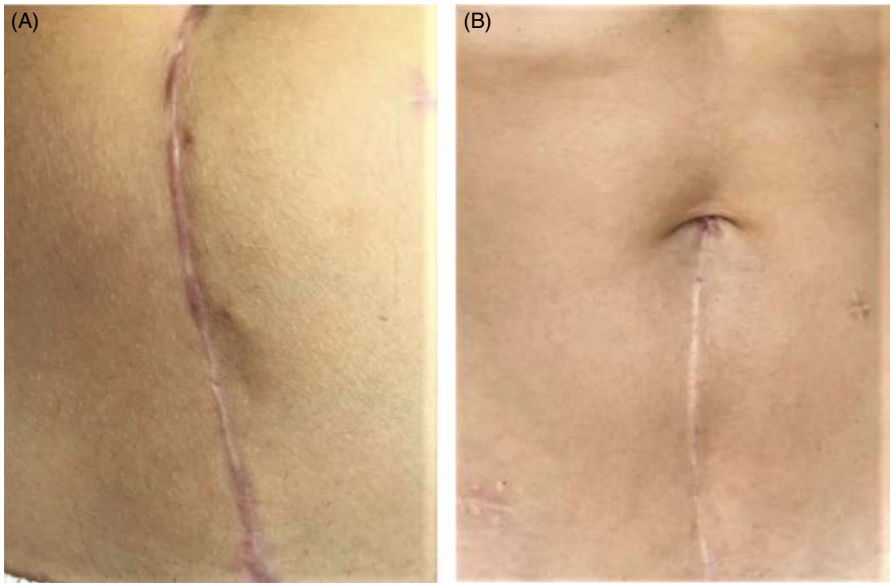

FIGURE 8 Treatment of postsurgical hypertrophic scar with multiple jet injections of HA (Profhilo, IBSA, Italy): before the treatment (A) and 6 mo after the treatment (B) flattening of the scar, release of the skin tension, and relief of the associated discomfort and pain (Courtesy of PerfAction Technologies)

In some exceptional cases, the wound healing aberrantly leads to development of hypertrophic scarring which can be reversed with jet-injected HA. Current recommendations for pharmaceutical management of hypertrophic scars and keloids attain uncontrolled cell proliferation, either with the cytotoxic antimetabolite or in combination with corticosteroid. However, the scars are known to be badly influenced by dehydration related to decreased presence of HA.[13] The fibrotic tissue of scars slowly invades dermal tissue and replaces its normal hydrating mechanism. Lack of proper hydration causes constant irritation, dryness, and itching and contributes to disease burden more than the high histamine level present in the scars.[36] The itching leads to inadvertent scratching and skin abrasion which further promotes cell proliferation and growth of the scar. Depth-controlled delivery of HA throughout the scar provides better hydration and results in immediate symptomatic relief (Figure 8).

Replenishment of the HA deficiency with exogenous HMW-HA was shown to normalize hyper-proliferation activity of keloid fibroblasts.[13] Increase in HA level promotes myofibroblast transformation from profibrotic to antifibrotic phenotype[37] and reduces the exaggerated and prolonged inflammation by acting on prostaglandin 2 secretion.[38] The bio-modulatory mechanism of hyaluronic acid normalizes fibroblasts activity instead of nonspecifically suppressing the cell activity by antimetabolites. The change in the cell behavior from uncontrolled hypertrophy to regeneration results in a therapeutic effect unlike the palliative effect of steroids.[39]

The physical impact of the jet's forceful penetration causes instant localized blanching and leads to immediate and at least temporary shutdown of the excessive microcirculation typically present in hypertrophic scars.[40] By limiting the capillary perfusion and thus decreasing oxygen supply, the effect is similar to the beneficial action of silicone sheeting. However, its action is distributed differently over time and in a much milder way in comparison to the high-pressure jet. At the same time, the jet delivers more uniformed spread of HA than a regular needle, therefore avoiding skin atrophy typically associated with steroids being injected too superficially.

6 | SAFETY AND TOLERABILITY

Jet injections of HA are associated with a low degree of discomfort providing tolerability and better acceptance of the treatment procedure.[22,27,28,30,32] Rapid skin penetration (average measurement of 30 ms, unpublished data of the EnerJet manufacturer) delivers low stimulation of nociceptors and lessens injection pain. Comparing to the vertical cutaneous damage by needle injection, the jet scatters HA micro-droplets sidewise and preserves normal

skin architecture without overstretching and subsequently minimizing discomfort.[30]

Adverse events related to jet injection of HAs are rare and limited to occasional bruising associated with miscalculated and excessive injection pressure. While maximal at the penetration point, jet's kinetic energy diminishes with dispersion of HA inside the skin. The micro-droplets still preserve enough power to advance but lack sufficient energy to penetrate into the tunica adventitia and basal lamina of the vessel wall. Therefore, at properly adjusted injection pressure, the possibility of intra-arterial injections can be completely dismissed. Published histology data demonstrate dispersion of HA without injuring cutaneous microcirculation or other dermal structures.[6,14,17] However, if the injection pressure is set accidentally too high, HA's dispersion occurs unnecessarily deep and the injury to the superficial small vessels may result in minor bruising.[30,32] Careful adjustment of injection parameters is essential, especially for older patients as the looser subcutaneous layers may favor deeper than intended dispersion of pressurized material.

Additionally, excessive injection pressure increases the risk of UV-stimulated melanin overproduction and postinflammatory hyperpigmentation (PIH) in high skin photo type. Inadvertent high impact leads to acute inflammatory reaction at the injection site and localized hyper-melanosis. However, the published rate of PIH incidents in jet-treated population is low and mainly related to incorrect treatment technique and poor patient education.[22,27]

7 | LONGEVITY OF EFFECT

For jet-injected HA, longevity of its clinical effect relates to the dual nature of the action mechanism, as discussed above. Biochemical properties of hyaluronan guarantee the initial customer-pleasing effect of skin hydration and volumization, but an unavoidable effect of hyaluronidase and ROS makes these benefits short-living, irrespective of HA concentration or cross-linking method.[12] The "true" clinical effect is determined by the generated tissue microtrauma and activated synthesis of ECM components. Although published data rarely report the treatment results beyond the 6-month efficacy,[26,28,30,32,33] Levenberg[27] demonstrated improvement in Fitzpatrick-Goldman wrinkle scale up to 18 months which was explained by continuous reorganization of the collagen during the final phase of the wound healing process.

8 | CONCLUSION

Although pneumatic delivery of a hyaluronic acid by liquid jet has a limited use in clinical practice, this treatment approach has a strong potential for extended implementation in esthetic dermatology. The jet-induced micro-trauma enhances modulation effect of hyaluronic acid and to more pronounced cutaneous regeneration. The synergistic mechanism has significant advantages of predictable and rapid clinical outcomes with a low discomfort. Additional well-designed investigations are required for establishing a scientific foundation and guidelines for this treatment modality.

DATA AVAILABILITY STATEMENT

(a) Publications referred to in this review are available and derived from public domain resources of National Library of Medicine (www.pubmed.com). (b) Technical data related to the described device is available on request from the corresponding author. The data are not publicly available due to commercial restrictions of PerfAction Technologies, the manufacturer of the described device.

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How to cite this article: Vinshtok Y, Cassuto D. Biochemical and physical actions of hyaluronic acid delivered by intradermal jet injection route. *J Cosmet Dermatol*. 2020;00:1–8. https://doi.org/10.1111/jocd.13674