Safety of the EnerJet treatments: current updates

White paper

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1 Introduction

Patients demand for cosmetic improvement is constantly increasing, with equal concern for efficacy and safety of the treatment. Implementation of jet-injections for intradermal administration of medications makes the treatment almost pain-free and do not expose patients to long-term side effects. Pneumatic jet device EnerJet is associated with a low degree of discomfort providing tolerability and better acceptance of the treatment procedure. Safety of EnerJet treatments is determined by two components: safety profile of the injected substance and the safety related to the injection process. Since the jet injection causes practically no significant pain even in the absence of any anesthesia, the likelihood of any damage resulting from the treatment is highly unfeasible.

As a jet–injecting device, EnerJet can be implemented for superficial needle-free administration of a variety of therapeutic injectable materials. So far, the most used one is hyaluronic acid (HA), a naturally occurring linear polysaccharide, widely distributed in human tissues. HA acts as a scaffold for the extracellular matrix, providing rigidity, hydration and turgor whilst regulating cellular movement and regeneration. [Triggs-Raine 2015] Due to their efficacy and safety, HA-based dermal fillers have become a “gold” standard and the most common type of filler currently used in aesthetic medicine. Anti-inflammatory, antioxidant and wound healing properties of HA were also found efficient for treatments of orthopedic, ophthalmological and pulmonary conditions. [Fallacara 2018]

2 Liquid jet injection with EnerJet

The EnerJet device creates a thin jet of pneumatically-accelerated fluid that is capable of penetrating the epidermis through a very small entry point (estimated as 200 microns) and causing a controlled dispersion into the superficial tissues. The dispersion occurs in a fan-like pattern, spreading from a single stagnation point into multiple directions. [Arora 2008, Park 2015] The width and depth of the material spread is controlled by the pressure and volume of injected fluid set by the device operator. Published evidence shows the depth of depositions ranging from papillary and reticular dermis to subcutaneous fat and distribution across the different skin layers [Mashiko 2015, Erlendsson 2019]. Since the thickness of the different superficial tissues (epidermis, dermis, subcutaneous fat, fascia

and muscles) varies greatly, the selected settings will insure penetration to the appropriate depth. The choice of the appropriate depth is to be determined by the operating physician according to the patient needs.

3 Safety mechanism per indication

Acne scars
In the treatment of acne scars, the EnerJet-produced jet of liquid hyaluronic acid is injected directly into the bottom of the scar. As a naturally-occurring glycosaminoglycan with main function of the skin restoration, HA has a proven clinical safety and provides regeneration and filling effect. The spread of the HA particles causes a spherical diffusion of the material into the scar and generates microscopic traumatic channels through the tissue fibers, which loosen the fibrotic scar structure. The result is comparable to manual surgical subcision but without typical swelling, bruising, and pain since the degree of tissue trauma is much lower.

Hypertrophic scars and keloids
EnerJet injection delivers more effective infiltration and more uniform spread of the material than a regular needle which allows avoiding thinning and atrophy of the skin, capillary dilation, and development of secondary hypopigmentation – typically associated with steroids being injected into a scar too superficially. [Perdanasari 2014]

A small number of local scar ulcerations observed in the group of hypertrophic and keloid patients treated by Levenberg (Table 1) were caused by the known dermal adverse effect of injected steroid triamcinolone acetonide. In order to prevent these complications, it is recommended not to exceed the dose of steroid recommended for treatment of keloids (60 mg/ml).

Dermal thickening and wrinkles
For the treatment of non-scarred tissue (such as atrophic aging skin) the safety of injections is determined by the intradermal dispersion after the liquid materials penetrates through epidermis. The spread of the liquid particles allows avoiding macro injury to the dermis and the microvasculature within the dermis.

Tolerability and procedural pain
EnerJet treatments are associated with minimal pain and discomfort. Table 1 presents a summary of the treatment tolerability based on the published data. The mechanism of the low pain can be associated with the high velocity of the jet and dispersion of the injected material. The rapid time at which high-speed liquid jet penetrates the skin (average measurement of 30 ms, unpublished data) produces low stimulation of nociceptors and lessens the pain. Compared to the traditional needle injection which produces a uniform vertical damage, the jet disperses immediately after penetrating the epidermis loosing

pressure while the particles are scattered across the dermis or the deeper layers. The dispersion does not produce overstretching of the tissue and avoids blood vessels and nerves, and subsequently minimizes the factors associated with pain and discomfort.

Pain is a factor that should be taken into consideration for the treatment of hypertrophic scars and keloids. The high injection pressure required for the drug to penetrate deep into the core of the scar is associated with a higher physical impact on the tissue compared to normal skin. The feeling is usually patient-specific and relates to the individual threshold of pain. In order to overcome this complaint, it is standard practice to add local anesthetic lidocaine into the injected solution.

Table 1. Review of pain and tolerability associated with EnerJet treatments

Title	Indication	# Pts	Pain level
Levenberg A et al. *Int J of Derm* 2010.	Skin aging, wrinkles	34	"The procedure was well tolerated by all participants… The overall patient satisfaction rate of over 80% demonstrates the tolerability and effectiveness of the treatments… The low downtime and prolonged improvement provide an attractive treatment option for dermal restoration."
Mashiko T et al. *Derm Surg* 2015.	Facial laxity	30	"The mean pain score using visual analog scale (VAS) was 2.0. No serious complications (e.g., intense postoperative pain, local irritation, persistent erythema, apparent bruising, nerve injury, skin necrosis, or foreign body reaction) occurred."
Lee JW et al. *Derm Surg*, 2010.	Acne scars	10	"Six patients reported no pain, and four reported mild pain during the procedure".
Kim BJ et al. *Derm Surg*, 2009.	Atrophic scar	1	"The patient did not report any pain or discomfort during the treatment."
Han TY et al. *Derm Surg* 2011	Skin aging, neck wrinkles	12	"In all cases, participants tolerated the procedure well, reporting only minimal pain and discomfort during treatment sessions."
Patel T. *J Drugs Dermatol* 2015	Acne scars	2	"The treatments were well accepted by the patients who reported mild during treatments even without applying an anesthetic prior to the treatment…. a unique, advanced technology for a safe and effective acne scar treatment with minimal downtime, pain, or side effects"

Cassuto D. 2014 (unpublished white paper)	Stretch marks	1	"The treatment was well accepted by the patient who reported mild pain during treatments even without applying an anesthetic prior to the treatment. The treatment is associated with minimal downtime, pain, or side effects."
Levenberg A. 2015 (unpublished white paper)	Keloid	6	"Treatment tolerance in all patients was good and with no pain during the treatment sessions."
Espinoza L et al. *J Cosmet Dermatol* 2020	Skin remodeling	34	"All patients tolerated the treatments well… All patients reported low degree of discomfort which contributed to their tolerability and acceptance of the treatment procedure."
Levenberg A et al. *J Cosmet Dermatol* 2020	Keloids	21	"Treatments were well-tolerated by all patients at mean injection pain of 2.0±1.0 (1-10 NPRS score). No severe adverse reactions or systemic side effects were documented."

Accidental release of shots

Unlike other therapeutic energy-based devices, the risks of accidental jet ejection and injury to patients or operator are highly unlikely with EnerJet 2.0, if not impossible. As the laser device emits the light beam, it is extremely intense and capable of injuring tissues even when held at large distances [US FDA 2018]. EnerJet device focuses its stream of ejected fluid right at the end of the nozzle. Unless the nozzle is placed firmly at the intended injection site, there will be no skin penetration by the emitted jet. Therefore, if an accidental aerial firing is made toward the patient or by-standing personnel, there will be no consequences since the jet won't have the energy necessary to penetrate.

4 Current safety data

Pre-marketing safety data

In-house histology studies (data on file, 2008) demonstrated that following the needle-free injection, a uniform spread of the material is achieved and normal skin architecture is preserved without injury to blood vessels.

Published ex-vivo trials with injected contrast material, showed the liquid contrast being dispersed as multiple vacuoles of different size and shapes (from sigmoid to round or ovoid), without injuring blood micro-vasculature or other dermal structures. [Cho 2017] The micro-circulation was shown to be intact, with the spread of the contrast around them. [Kwon 2016, Erlendsson 2019]

Literature review

Review of the EnerJet-related articles, case reports and unpublished white papers was performed in order to summarize the safety aspects of the EnerJet treatments. It includes the treatments of various dermatological and aesthetic conditions performed in many body areas, from facial regions to torso. The findings are summarized in Table 2.

Table 2. Literature review of EnerJet safety data

Sourse	No. patients/ skin type	Treated area	Medication	Follow-up period	Adverse events
Levenberg A et al. *Int J Dermatol* 2010	34/ Fitzpatrick I-IV	Dorsal hands, chest, neck, face	HA*	Up to 18 mo.	Pinpoint bleeding, transient erythema and edema, focal tenderness resolved within 24h and 1 case of post-inflammatory hyperpigmentation (PIH).
Mashiko T et al. *Derm Surgery* 2015.	30/ Non-specified	Temporal hairline, malar prominence	HA + 20% glucose	Up to 6 mo.	2 cases of PIH.
Lee JW et al. *Derm Surgery* 2010.	10/ Fitzpatrick II-V	Face	HA	3 mo.	Transient spot bleeding at entry point, slight edema resolved within 48 hr.
Kim BJ et al. *Derm Surgery* 2009.	1/ Non-specified	Forehead	HA	6 mo.	Entry point bleeding, slight edema resolved within 48 hrs.
Kobus KF et al. *Aesthetic Surg J* 2010.	20/ Non-specified	Periorbital, forehead, neck, upper lip region, nasolabial folds	HA	6 mo.	None
Han TY et al. *Dermatol Surg* 2011.	12/ Fitzpatrick II-IV	Neck	HA	2 mo.	None
Landau M. 2014 (unpublished white paper)	1/ Fitzpatrick III	Décolleté	HA	6 mo.	None
Patel T. J *Drugs Dermato*, 2015.	2/ Fitzpatrick IV-V	Face	HA	3 mo.	Transient bumps and spot bleeding at entry points

Cassuto D. 2014 (unpublished white paper)	1/ Non-specified	Back	HA	Up to 3 yrs.	Transient bumps and spot bleeding at entry points.
Levenberg A. 2015 (unpublished white paper)	6/ Non-specified	Breast, chest, back, peri-auricular	CS	6 mo.	Bleedings at the entry points and a slight edema resolved within 48 hours
Artzi O. *Clin Dermatol J*, 2017.	11/ Non-specified	Palms, armpits	Botulinum toxin	1 mo.	None
Naranjo P et al. *J Cosmet Laser Ther* 2019	3/ Non-specified	Upper lip	HA	6 mo.	None
Espinoza L et al. *J Cosmet Dermatol* 2020	34/ Non-specified	Middle and low facial regions	HA	3 mo.	Three patients (8%) had minor bruises along with transient swelling and erythema.
Levenberg A et al. *J Cosmet Dermatol* 2020	21/ Non-specified	Face, torso, upper extremities, ears	CS + 5-FU	3 mo	Self-healed superficial lesion ulcerations were observed in 4 patients (19%)

*HA – hyaluronic acid, CS – corticosteroids, 5-FU – fluorouracil

Post marketing survey

In 2019, PerfAction Technologies conducted post-marketing survey among current EnerJet users in order to receive their feedback on efficacy and safety of the treatments performed with EnerJet.

The targeted clinicians (dermatologists, aesthetic doctors, plastic surgeons and general practitioners specializing in aesthetic medicine) use EnerJet as part of their routine medical practice. Twenty-five users from 17 countries worldwide responded to the on-line questionnaire. The questionnaire included 17 questions divided in two groups – related to the treatment of acne scars with hyaluronic acid and treatment of keloids with steroids. Overall, the number of the patients treated for acne scars was approximated as 475, and for keloids – 300. Safety was assessed according to the reported adverse events and the data was divided in two groups – short-term events (documented during or immediately after the treatment) and long-term events (documented several months after the treatment). The reported adverse events associated with the treatment of acne scars were either related to incorrect treatment technique or to insufficient patient care, or were the treatment-expected downtime phenomena (Tables 3). The adverse events reported

adverse events associated with the treatment of keloids have been mainly related to the treatment technique or to the nature of injected drugs (Tables 4).

Table 3. Respondents reporting adverse events associated with EnerJet treatment of acne scars

Adverse event (longevity)	Downtime phenomena (respondents %)	Faulty treatment technique (respondents %)	Faulty post-treatment care (respondents %)
Hematoma, bruises (short-term)	0	13%	0
Infection (short-term)	0	0	8%
Local edema (short-term)	4%	0	0
Hyperpigmentation (long-term)	0	0	4%
Local papules, erythema and bleeding points (short-term)	8%	0	0

Table 4. Respondents reporting adverse events associated with EnerJet treatment of keloids

Adverse event (longevity)	Downtime phenomena (respondents %)	Faulty treatment technique (respondents %)	Faulty post-treatment care (respondents %)
Pain (short-term)	0	5%	0
Atrophy, enhanced micro-vessels (long-term)	0	0	5% (associated with the injected drug)
Ulceration (long-term)	0	0	5% (associated with the injected drug)
Erythema, edema (short-term)	5%	0	0

Overall, adverse events were reported only by a small number of the respondents. They happened irrespectful of the respondents' experience with EnerJet. The complications were mainly reported as occurred during or immediately after the procedure. A small number of the long-term events were related to the side effects of the injected substances.

In-house clinic safety data

During the 2016-19 period, the PerfAction's own in-house clinic performed 688 EnerJet treatments on 113 patients (M/F = 6/107) seeking skin rejuvenation, non-surgical face lift, and correction of dermal wrinkles and scars (acne scars, striae albae, post-op hypertrophic scars). The treatments were performed with injecting diluted HA fillers. Topical anesthetic cream or skin moisturizer was used to prepare skin before injections. The treatments provided good results to patients' satisfaction. A total of 20 treatments (3 %) had minor side effects ranging from bruising to hyperpigmentation (Table 5).

Table 5. Distribution of side effects among the in-house treated population.

Side effect/Longevity	Cases	% per treatments
Bruising (short-term)	11	2%
Local edema (short-term)	2	0.3%
Hyperpigmentation (short-term)	2	0.3%
High pain (short-term)	1	0.1 %
Infection (short-term)	1	0.1%
Long-lasting bumps (long-term)	2	0.3%

The distribution of the adverse events is similar to pattern observed in the 2019 post-marketing survey. Most of side effects were short-term (less than one week). They were caused by excessive pressure parameters chosen by the operator who decided to override the system software. Additionally, we observed persistent appearance of skin papules when the injected HA was slow to integrate in tissues due to its rheological properties.

5 Analysis of the safety data

Downtime-related events

The jet injection is associated with several immediate skin phenomena. Penetration of the skin leaves tiny pin-prick marks indicating the jet entry point. Intradermal deposition and spherical dispersion of the injected material raises the skin into a skin papule. Mechanical impact to the skin causes microvasculature vasodilation and skin erythema. All these phenomena are short living and self-resolved within few hours except the skin scabs formed at the entry point. Skin scabbing is observed after each injection and resulted from the miniscule damage to the superficial capillary plexus. As the stream of injected fluid enters into the skin, it creates a penetration channel through the capillary network in superficial dermis with the channel. Due to the tissue resistance contra-pressure, the capillary blood is pushed through the channel out to the skin surface where

it coagulates, dries and peels off in a few days. These phenomena are the expected signs and criteria of the material penetrating and dispersing inside the skin and should be seen as the treatment expected downtime.

Expected adverse events

On the other side, the adverse events associated with EnerJet treatments are rare and limited to occasional bruising and pin-point post-inflammatory hyperpigmentation. These are the expected adverse events and mainly associated with miscalculated use of excessive injection pressure.

During the rapid time at which the high-speed liquid jet penetrates the skin, it applies pressure on the soft tissues and compressed intradermal blood vessels decreasing the chance of post-treatment bruising. However, if the injection pressure is set accidently too high, the jet dispersion occurs at unnecessary low depth and the injury to the superfiscial small vessels may result in bruising. Minor bruises and occasional hematoma are considered the expected adverse evnets and are related to incorrect treatment technique. The bruising can either resolve spontaneously or be treated topically. In order to prevent this adverse event, operator of EnerJet should adjust the pressure by carefully increasing the pressure parameters until the end-point of the treatment (dermal papule) is achieved.

Additionally, excessive injection pressure could increase the risk of pinpoint post-inflammatory hyperpigmentation in high skin photo type. Hyperpigmentation is caused by post-treatment overproduction of skin melanin and can be related to exposure to the direct sun lights after the treatment. In order to prevent localized pigmentation, physician must instruct the patient to use sunblock creams or avoid tanning in the immediate post-treatment period.

Lack of vascular or nerve injury

Any type of injections, weather using needles or cannulas, has been associated with several kinds of adverse events. Vascular damage has been described after injections with both needles and cannulas [Sito 2019]. Vascular can be venous or arterial. Pneumatic jet injections on the other hand, have never being reported to cause any vascular accident during the last 10 year of active use. It has been demonstrated extensively in different histological trials that the jet is capable of dispersing the injected material uniformly in the skin and superficial subcutaneous tissues surrounding the blood vessels without ever been capable of injuring them [Levenberg 2010, Mashiko 2015, Erlendsson 2019]. It can be explained by the mechanism of jet propagation in the tissues. As the highest jet energy is concentrated when the jet penetrates the skin surface, it is immediately dispersed in the epidermis and the superficial dermis as the jet particles spread in the skin. At this point the dispersing particles still preserve enough kinetic energy to advance through the tissues but they lack sufficient energy to penetrate into the tunica adventitia and basal lamina of the vessel wall. Therefore, we can completely dismiss the possibility of intra-

arterial injections when the injection pressure is properly adjusted. However, one cannot rule out a marginal injury of the small superficial veins that is of a little concern except for the possibility of very minor bruising.

The nerves anatomically are positioned at deeper layers and cannot be reached by the jet particles. Kinetic energy of the dispersed particles is not high enough to cause even the slightest risk of injury.

Infection

Infection can be caused by lack of aseptic technique during the treatment or when the treated area is infected by the patient after the treatment. In order to prevent intra- and post-treatment infection, physicians must maintain the same aseptic technique as required for traditional needle injections.

6 Conclusion

For the last 10 years of active practical use, EnerJet device demonstrated its safety profile. Overall, the safety of the EnerJet treatment injections is determined by the jet's physical impact on the tissue or is affected by the safety profile of the injected material. This has being verified clinically and histologically with different kinds of injectable therapeutic materials and for various clinical indications. The safety features of EnerJet are confirmed by the fractional rate of the accidental injuries reported by more than 100 users around the world. The high tolerability of the treatments adds a further confidence to its incapability of causing damage whatsoever.

7 References

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