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ORIGINAL CONTRIBUTION

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High-velocity pneumatic injection of non-crosslinked hyaluronic acid for skin regeneration and scar remodeling: A retrospective analysis of 115 patients

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Abstract

Background: Pneumatic-assisted high velocity jet injections are an alternative method for intradermal delivery of hyaluronic acid (HA) and demonstrated efficacy in dermal thickening and scar remodeling with minimal side effects.

Aims: We aimed to investigate the clinical efficacy comparing non-crosslinked HA (NCL-HA) and crosslinked HA (CL-HA) for aesthetic skin concerns.

Methods: We retrospectively analyzed charts of 115 patients treated with jet injected NCL-HA and CL-HA for skin rejuvenation, age-related laxity and rhytidosis, hypertrophic and acne scars and striae.

Global Aesthetic Improvement Scale (GAIS) and the 5-grade patient satisfaction scale were used for assessment of the treatment efficacy at the 3-month follow-up. Efficacy was separately analyzed between patients receiving NCL-HA vs. CL-HA. Longevity of treatment effect was measured by the time to voluntary return for repeat treatment.

Results: An average of 2.8 treatments was completed per patient with a low incidence of side effects including bruises (7%) and temporary local edema (1%). Patients were highly-satisfied with the treatment results in all categories with the average satisfaction scores of 3.68 (NCL-HA) and 3.76 (CL-HA). An average GAIS score of 1.7 ("much improved") was calculated for neck, décolleté and perioral areas. An overall GAIS score averaged as 1.78 (NCL-HA) and 1.6 (CL-HA). Longevity of the effect averaged 13.1 months for NCL-HA and 13.2 months for CL-HA groups.

Conclusion: Our retrospective data showed similar significant improvement of all aesthetic skin concerns in 115 subjects treated with either NCL-HA or CL-HA delivered intradermally by a high velocity jet-injector device with minimal downtime, pain or side-effects.

KEYWORDS

enerjet, hyaluronic acid, pneumatic jet injection, scar remodeling, skin regeneration

1 | INTRODUCTION

Injection of hyaluronic acid (HA) has become a standard procedure worldwide in esthetic medicine to provide soft tissue augmentation, enhance facial rejuvenation, and correct soft tissue defects.[1] In addition to the viscoelastic and filling properties, HA's provide essential hydration to the skin and enhance the synthesis of components in the Extracellular Dermal Matrix (ECM).[2,3] However, the natural

degradation mechanism limits endogenous HA half-life to 24 hours.[4] Quick loss of its properties can be overcome through crosslinking stabilization of exogenous HA or by enhancing efficacy with regenerative mechanisms occurring in the skin.[5]

There are a number of common HA delivery methods, including traditional needle injections and microneedling. Microneedling injection of non-crosslinked HA has been shown to cause therapeutic micro-trauma which stimulates a repair response and induces collagen production.[6] This effect, however, is limited to the superficial dermis and associated with bleeding, swelling, and infections.[7]

Alternatively, pneumatic-assisted high-velocity jet injections of liquid HA has demonstrated efficacy in dermal thickening and scar remodeling with minimal side effects.[8-10] A controlled accelerated dispersion of HA micro-droplets creates multiple micro-injuries to the surrounding dermis and activates repair mechanisms. As a result, the stimulation of fibroblasts and increase in collagen production provides long-term skin augmentation and remodeling.[11,12]

We present a retrospective analysis of our clinic's experience in the administration of both non-crosslinked HA (NCL-HA) and crosslinked HA (CL-HA) using a pneumatic jet injection device (EnerJet, PerfAction Technologies, Rehovot, Israel) in 115 patients for esthetic skin concerns.

2 | METHODS

We retrospectively analyzed charts of 115 patients treated with jet-injected HA in an established esthetic clinic (Ontario, Canada) between July 2008 and July 2018. Patients with incomplete data (partial assessments, lost to follow-up) were excluded from the analysis in the initial review of all patient charts. The treatments were performed for skin rejuvenation, age-related laxity and rhytidosis, acne scars, stretch marks (*striae albae*), and hypertrophic scars. Patients with vascular disorders, coagulopathies, or pregnant/lactating females were not indicated for the treatment. All the patients signed an informed consent.

2.1 | Materials and treatment procedure

Jet injection of HA is a delivery method for which a pneumatically operated device generates an accelerated stream of HA solution for epidermis penetration and subsequent dispersion within the dermis. The dispersion depth is proportional to the power of injection pressure and controlled by the device software.[11,13] The widespread of HA in tissues, documented as an average 1 cm in diameter, has been also found to be beneficial.[10]

In our practice, we used the computerized jet-injector AirGent and its later version EnerJet (both by PerfAction Technologies, Rehovot, Israel). Both devices have the same technology for which a pneumatically operated piston applies pressure on a liquid in the reservoir so that it is ejected as a stream at a velocity high enough to penetrate the skin.

Each treatment was performed as a series of injections in 1-cm steps over unscarred skin or hypertrophic scars, or as a single injection into each depressed acne scar. Prior to the procedure, topical anesthetic cream (EMLA, Astra Pharmaceuticals, LP) was routinely applied in order to lower expected treatment discomfort. The device allowed for controlling injection volume and the depth of penetration by adjusting software parameters, namely injection pressure, and volume. The volume of each injection ranged between 0.05-0.75 mL and the pressure was adjusted according to the regional dermal thickness. Each injection produced a temporary intradermal papule 8-10 mm in diameter and 2-3 mm in height. The papule indicated dispersion of the injected HA inside the skin. After the procedure, patients received instructions for avoiding sun exposure in order to prevent post-injection pigmentation. Adverse events were documented during and after each treatment. Treatment tolerability was assessed by asking the patients to rate injection pain according to the 1-10 Numeric Pain Rating Scale (NPRS). The course included 3 monthly treatments, repeated later as voluntary maintenance, as patients perceived the effects diminishing.

The treatment was initially implemented with a crosslinked HA (22.5 mg/mL, Esthélis Basic, Anteis, Lonay, Switzerland). Looking to extend the range of jet-injected materials, we tried and achieved efficacy with the pharmacy-prepared non-animal derived non-crosslinked HA (10 mg/mL, York Downs Chemists). Both HA gels were diluted with normal saline to a final concentration of 2.5 mg/mL, empirically corresponding to an optimal viscosity level suitable for achieving skin penetration.

2.2 | Assessment of treatment results

As a routine practice, the patients were photographed before the first treatment and as much as possible after treatments when patients returned for a 3-month follow-up visit. We also asked them to grade treatment satisfaction as “not satisfied at all (1)”, “not satisfied (2)”, “neutral (3)”, “satisfied (4)”, “very satisfied (5)”. Upon analysis, the photographs were compared by two esthetic physicians employed in the clinic and the treatment outcomes were rated on the 7-grade Global Aesthetic Improvement Scale (GAIS) as very much improved (3), much improved (2), improved (1), no change (0), became worse (−1), became much worse (−2), became very much worse (−3). We reviewed longevity of the treatment effect by analyzing the time to voluntary return to repeat the treatment. Additional comparative analysis of the treatment efficacy was performed between the patients treated with crosslinked and non-crosslinked HAs.

3 | RESULTS

Data from a total of 325 treatments performed on 115 patients (all female, average age is 48.6 years old) were analyzed. An average of

2.8 treatments was completed per patient, performed in 4-6 weeks of each other. Average follow-up visit after the treatment series was at 2.7 months. The average time to voluntary repeat treatment after the initial series was 13.1 months (NCL-HA) and 13.2 months (CL-HA).

The treatments were tolerated well. The average injection pain was scored 2 on the NPRS scale. There was a low incidence of side effects which include self-resolved bruises and temporary local edema occurred at low incidence (7% and 1% of the treatments, respectively).

Post-treatment images compared to baseline demonstrated an improvement in all treated areas which matched the patients' satisfaction with the treatment results (Figure 1). An average GAIS score of 1.7 ("much improved") was calculated for neck, décolleté, and perioral areas.

Patients noted increased elasticity, turgor, and improved general appearance of the skin, especially in the dorsal hands and décolleté, as well as smoothing of the wrinkles in perioral and cheek areas. (Figures 2,3) Among the treated scars, improvement and high patient satisfaction were achieved in all scar categories. (Figure 4).

Sixty percent of the patients treated for skin laxity and rhytidosis returned seeking repeated treatments. Longevity of the effect calculated as the time between initial and maintenance treatments averaged 14.4 months (Table 1).

4 | DISCUSSION

We conducted a retrospective analysis of patients treated with needle-free pneumatically accelerated jet injections using mainly non-crosslinked HA. Investigation of the clinical efficacy of non-crosslinked HA for esthetic skin concerns is rather limited and mainly associated with superficial microneedling injections. Microneedling appears to initiate the natural inflammatory cascade that occurs following any skin trauma.[7,14] The healing process originated from the jet-induced micro-injury is similar. Propulsion and dispersion of HA droplets cause stretching of the surrounding skin and activation of dermal fibroblasts.[10,15,16] The mechanical tension converts dermal fibroblasts into myofibroblasts by the induction of mechano-responsive genes, accelerates fibroblast proliferation, and inhibits apoptosis.[17] It has been demonstrated that jet-injected CL-HA activates synthesis of new collagen type I and III up to 4 months after injection into the skin[10,18] with beneficial effects on facial wrinkles[10,19-21] and acne scars.[9,22]

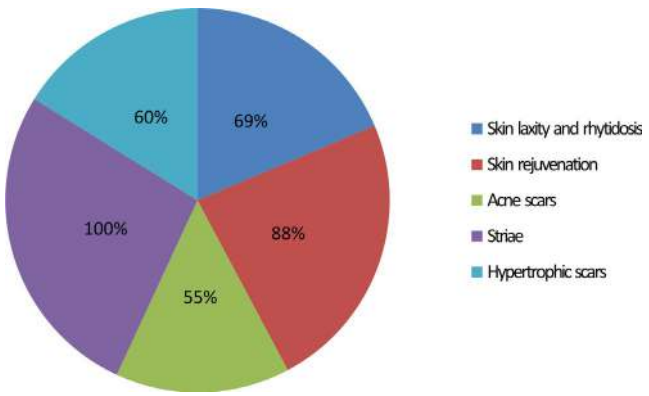

FIGURE 1 Proportion of patients from both NCL-HA and CL-HA groups satisfied with treatment results (satisfaction score ≥ 4)

Comparative studies by Wolhrab[23] demonstrated that NCL-HA produced the same proliferative effect on dermal fibroblasts as the chemically crosslinked HA (CL-HA). Our experience also demonstrated clinical improvement in aging skin and in dermal scars, mostly using NCL-HA. The physician-assessed results revealed reduction of skin rhytidosis, increased skin thickening, improved appearance of atrophic scars, and flattening of hypertrophic scars.

Due to the natural process of degradation, the clinical effects of NCL-HA delivered by microneedling[24] or pressure infusion[25] are short-lived. Nevertheless, we observed improvements using NCL-HA with the EnerJet device (Figures 2, 3) sustained up to and beyond 12 months after treatment. This led us to conclude that the efficacy was due to the combination of the high-velocity jet-generated micro-trauma along with the biological characteristics of HA, irrespective of its level of crosslinking.

However, this dual mechanism may be also applicable to the scar treatment. The jet-induced bursts of HA help to break the fibrotic strands, while exogenous HA appears to normalize hyperproliferation activity of scar cells and provide hydration to HA-deprived tissue[26] resulting in softening and shrinking of the hypertrophic scars.[27] For atrophic acne scars, the jet impact releases the bottom of the scar from underlying tissues, while HA provides supplemental volume and completes the lifting effect of the scar.[22]

4.1 | Comparison between crosslinking and non-crosslinking groups

Although CL-HA is traditionally used for dermal injections, 85% of the patients in our group were treated with NCL-HA. Irrespective of crosslinking type, exogenous HA undergoes the same processes of dissociation of the polymer chains through enzymatic (hyaluronidase) and free radical degradations.[5] The depolymerization continuously yield low-molecular-weight fragments with pro-inflammatory properties and collagen-synthesis functions.[3,28] We assumed that the sub-clinical level of inflammation present in the skin after the injections could contribute to the treatment efficacy. In our comparative analysis between NCL- and CL-treated patients, no major differences were observed in the end-results. The average patient satisfaction score with NCL-HA and CL-HA treatments were 3.68 and 3.76, respectively; the average GAIS-1.78 and 1.6, respectively. Longevity of the wrinkles and laxity improvement was also similar with the average time to voluntary repeat treatment was 13.1 months (NCL-HA) and 13.3 months (CL-HA). However, rejuvenation with NCL-HA scored higher in the décolleté region, whereas

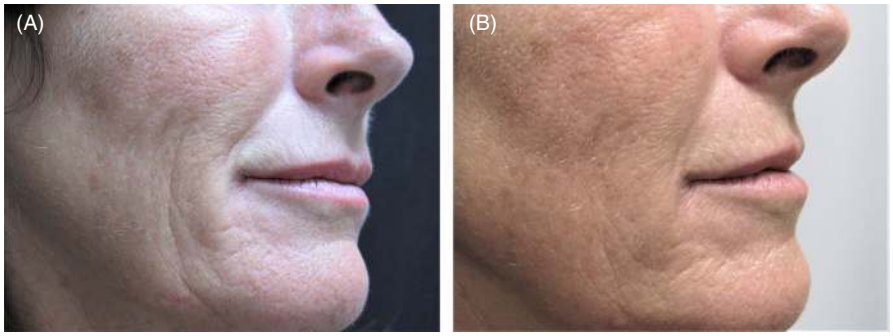

FIGURE 2 Treatment of the facial rhytidosis: before and 7 mo after the treatment

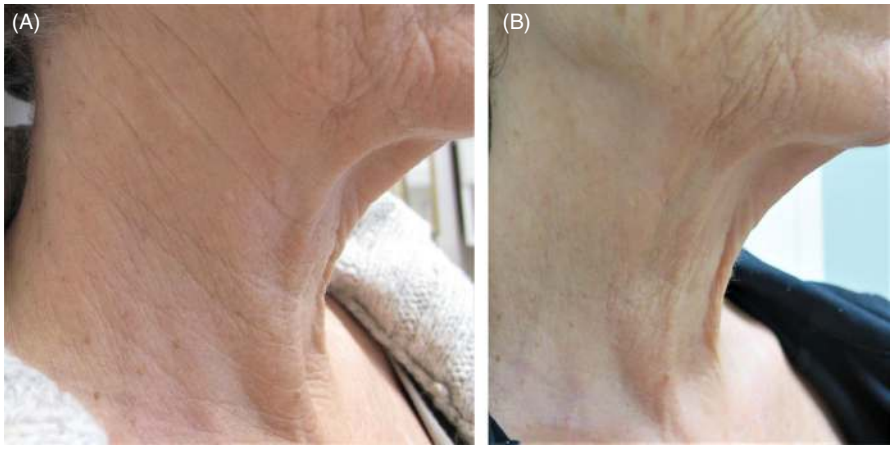

FIGURE 3 Treatment of the neck laxity and rhytidosis: before and 15 mo after the treatment

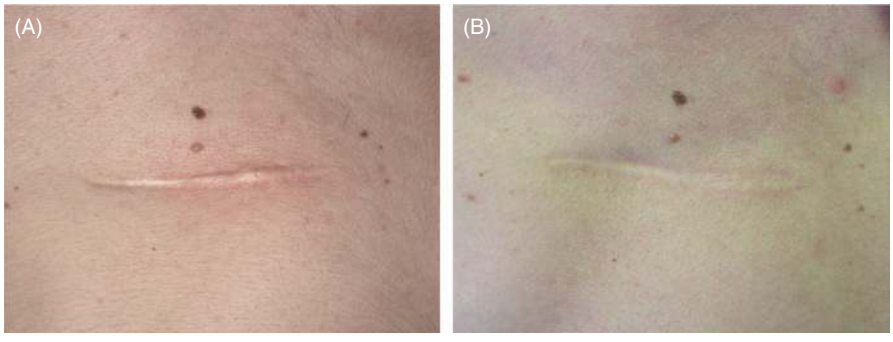

FIGURE 4 Treatment of postsurgical hypertrophic scar: before and 2 mo after the treatment

CL-HA was more effective in post-acne and hypertrophic scar treatments.

4.2 | Safety and tolerability

We did not find any difference between the HA types in the treatment safety. The treatments were associated with minimal pain and discomfort, even in the case of scars that required higher pressure parameters to achieve penetration compared to non-scarred skin. We assume that the high-velocity of the jet and immediate spread of HA droplets decreases impact to the skin resulting in less irritation. Only 8% of patients were documented with minor transient swelling, erythema, and bruising, which mainly occurred during the learning curve period. The technical improvements to the device helped minimize operator variability and contributed to further decrease adverse events over the 10 years of use.

4.3 | Limitations of this report

Although efficacy of NCL-HA has been shown to a certain extent in the literature, this is the first report demonstrating clinical synergy of jet injection and NCL-HA. However, the retrospective nature and absence of fully quantified data limits the statistical analysis of the results. Due to the difference in size of each of NCL-HA and CL-HA groups, we were unable to draw statistically significant conclusions. Although jet injections of NCL-HA became routine in our clinical

TABLE 1 Treatment regimens and efficacy results in various anatomical regions

Treated area	Number of patients	Average number of treatments	Average follow-up period, months	Average GAIS score[a]	Average patient satisfaction score[b]	Time to repeated treatment, months
Skin laxity and rhytidosis						
Cheeks	10	2.8	3.2	2.1	3.7	15.2
Upper Lip	7	2.9	1.3	1.6	3.3	14.1
Perioral	28	2.8	2.7	1.7	3.8	14.1
Neck	26	2.9	2.7	1.6	4	12.8
Skin rejuvenation						
Hands	10	2.8	2.5	1.3	3.9	n/a
Décolleté	7	2.9	2.8	1.7	4	7.3
Acne scars (facial)	28	2.8	3.5	1.9	3.9	n/a
Stretch marks (abdomen)	26	2.9	3	2	4.2	n/a
Hypertrophic scars (forearm, temple, abdomen)	10	2.8	2.5	1.8	3.8	n/a

[a]Very much improved (3), much improved (2), improved (1), no change (0), became worse (−1), became much worse (−2), became very much worse (−3).
[b]Not satisfied at all (1), not satisfied (2), neutral (3), satisfied (4), very satisfied (5).

practice, further investigation of this treatment modality would be beneficial.

5 | CONCLUSION

We retrospectively analyzed our experience using pneumatically accelerated jet injections of NCL-HA and CL-HA for the correction of various esthetic conditions over a 10-year-period in 115 patients. Combining the bio-modulating effect of HA with the regeneration effect of the tissue micro-trauma allowed for successful skin rejuvenation and scar remodeling with minimal downtime, pain, or side effects. Results independently assessed by both the investigators and patients showed improvements lasted on average 14 months without apparent clinical difference between crosslinked and non-crosslinked HA. The observed skin regeneration effect coupled with the benefits of the high-velocity jet-injector device would appear to provide an efficacious, user-friendly, and cost-effective treatment.

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DATA AVAILABILITY STATEMENT

The data supporting the findings of our article are available from the corresponding author on the written request. The data is not publicly available due to the ethical and privacy restrictions.

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