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ORIGINAL RESEARCH

Evaluation of the Efficacy and Safety of Injectable Non-Cross-Linked Hyaluronic Acid Associated with a Protective Buffer in Patients with Photoaging of the Periorbital Area

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Purpose: To evaluate the efficacy and safety of injectable non-crosslinked HA associated with a protective buffer in patients with photoaging, particularly in lateral canthal rhytids.

Patients and Methods: We conducted a post-market interventional clinical investigation in patients with lateral canthal rhytids graded between 1 and 4 based on the crow's feet grading scale who received a single session of the product in the periorbital area. The primary endpoint of this clinical investigation was improvement in hydration. Secondary endpoints included the evaluation of the product efficacy against lateral canthal rhytids and infraorbital dark circles, subjects' and investigator's satisfaction, as well as the occurrence of any adverse events. The follow-up was for 7 days.

Results: The study included 34 patients (6 male and 28 female) with a mean age of 53 ± 7.58 years. The mean corneometric index (CM value) increased from 57.17 ± 11.04 to 58.83 ± 7.36 ($p < 0.05$). Dynamic rhytids reduced by 6%, with a significant reduction in the crow's feet grading scale from 2.76 ± 0.69 to 2.59 ± 0.76 ($p < 0.05$). Infraorbital dark circles improved in 50% of patients. Patients' satisfaction was similar to the evaluators' satisfaction, with 74% of the patients rating the outcome as "improved" or " much improved", and 68% of evaluators rating the outcome as "improved" or "much improved" on the Global Aesthetic Improvement Scale (GAIS). Mild ecchymosis was the only reported adverse event.

Conclusion: Non-cross-linked HA associated with a protective buffer is an effective and well-tolerated treatment for the consequences of photoaging in the periorbital area.

Keywords: hyaluronic acid, hydration, wrinkles, skin quality, aesthetic improvement, photoaging

Introduction

The International Classification of Diseases (ICD) of the World Health Organization (WHO) recognizes skin photoaging as a pathological condition that is listed under the references L57 of the current ICD-10[1] and under EJ20 of the new ICD-11 revision.[2] Skin aging is a multifactorial biological process influenced by both intrinsic factors, such as genetics and cellular metabolism, and extrinsic stressors, including ultraviolet (UV) radiation and environmental pollution.[3–5] Extensive sun exposure results in so-called photoaging with similar pathological mechanisms as observed in normal and premature aging.[6] Skin aging occurs on a cellular and molecular level, including a decrease in the amount of hyaluronic acid (HA) in the epidermis, an increase in the binding strength of HA with the tissue structures in the dermis, and a reduction in the ability to extract HA from the skin.[7,8] Phenotypic changes in cutaneous cells as well as structural and functional changes in extracellular matrix (ECM) components are also part of the skin aging process, leading to wrinkles, loss of elasticity and moisture, dermal atrophy, and dermal laxity, decrease of skin integrity, skin tissue remodeling, and a gradual decrease of melanocytes with irregular melanin production.[6,9,10]

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The mechanisms of photoaging are complex and often overlap with changes due to natural chronological aging. Photoaging alters collagen and affects various skin components, such as anchoring fibrils, proteoglycans and glycoaminoglycans.[3] Its manifestation can vary depending on the specific skin area affected, inherent skin pigmentation, and individual genetic factors.[3,11]

Both intrinsic and extrinsic aging processes alter collagen and elastic fibers in a quantitative and qualitative manner.[6] Photoaging—or skin aging in general—is primarily influenced by the extent of UV exposure and the individual's skin phototype. UV radiation is the predominant driver of extrinsic ageing and causes wrinkles, decreased elasticity and moisture, dermal thinning, laxity, and pigmentary irregularities resulting from altered melanocyte function.[5,6,12–14] Because UV exposure is the major cause of these alterations, the term "photoaging" is frequently used interchangeably with extrinsic ageing.[5,14]

Those with a history of significant sun exposure, individuals living in high-UV geographic regions, and people with fair skin are most susceptible to UV-related skin damage.[7,8]

The visible symptoms, such as wrinkles, deep furrows, loss of skin tone, sagging and dry skin, rough-texture appearance, solar lentigines, and uneven pigmentation, are mostly discomforting for the patient. Sun-exposed areas of the skin, such as the face, neck, décolletage, hands, and forearms, are the sites where these changes occur most often.[15–17] One of the first areas with signs of aging is the periorbital area with the occurrence of lateral canthal lines, also called crow's feet.[18]

Several treatment options exist for photoaging, including the topical application of retinoids, chemical peels, cosmeceuticals, and injectable soft-tissue fillers.[15] Skin fillers are a widely used and effective method for facial rejuvenation. They enhance soft tissue volume, improve hydration, smooth wrinkles, and correct superficial imperfections. However, they do not address all signs of aging, such as reduced melanin production.[19] Hyaluronic acid (HA), a natural linear polysaccharide, is commonly used in fillers. When derived from bacterial fermentation, it typically does not elicit immune responses. HA can be used alone or in combination with other substances to promote skin rejuvenation.[20–22] It is also supposed to act as physical barrier or a scavenger of superoxide.[22] Depending on the treatment goal, either non-crosslinked (linear) or crosslinked HA is used. Non-crosslinked HA is primarily applied in skin restoration procedures for short-term benefits, such as enhanced hydration and fine line reduction, due to its high water-binding capacity. Crosslinked HA, with greater resistance to enzymatic and oxidative degradation, is preferred for longer-lasting results. It is typically used to fill wrinkles, restore volume, and remodel facial contours.[23]

Adverse effects associated with HA-based fillers are generally mild and transient, usually appearing within hours or days post-injection. While minor injection-site reactions are common, serious complications such as nodule formation, filler migration, and granuloma are rare and mainly associated with crosslinked HA.[20,24,25]

The investigational medical device is an injectable solution of non-crosslinked HA associated with a protective buffer marketed for application in various skin areas of the face and body.

In this publication, we present the results of our post-market interventional clinical investigation to evaluate the efficacy and safety of the device in subjects with photoaging, particularly in the periorbital area.

The primary endpoint of our clinical investigation was skin hydration status before and after treatment with non-cross -linked HA associated with a protective buffer, and the secondary endpoint evaluated the degree of lateral canthal rhytids (crow's feet) using the Crow's Feet Grading Scale, the severity of infraorbital dark circles using the photonumeric scale, and overall aesthetic improvement using the Global Aesthetic Improvement Scale (GAIS). Additionally, the study monitored adverse events and product deficiencies to ensure clinical safety.

Materials and Methods

We performed a single-center, non-randomized post-market clinical investigation on adult patients who received injectable HA (RRS® HA EYES, Skin Tech Pharma Group S.L.U., Spain) for the treatment of photoaging in the periorbital area between November 2022 and April 2023. The clinical investigation was carried out in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. All enrolled patients provided written informed consent.

Patient Selection

We included adult patients (male and female) over 18 years of age with lateral canthal rhytids graded between 1 and 4 on the Crow's Feet Grading Scale for both resting (static) and hyperkinetic (dynamic) facial expressions. Pregnant and breastfeeding women were excluded.

Study Design

After signing the informed consent, the patient's status was assessed, and their degree of skin photoaging was determined according to the degree of lateral canthal rhytids. An additional quantitative measurement of facial skin hydration was conducted using a Corneometer® CM 825 (Visit 1).

After the baseline assessment, patients received a single administration session of the investigational medical device in a satellite center on the same day (Visit 2). Patients were followed up for 7 days to assess the treatment effect and occurrence of any adverse events (Visit 3). The visit schedule is illustrated in Figure 1.

Study Objectives

The primary objective of this clinical investigation was to evaluate the efficacy of investigational medical device in improving the hydration of photoaged skin. The main endpoint used was skin hydration assessed with Corneometer® CM 825 as a measuring device.

Secondary objectives included the evaluation of the product efficacy against skin photoaging using Crow's Feet Grading Scale for both resting (static) and hyperkinetic (dynamic) facial expressions.[18] Further secondary endpoints were the evaluation of the aesthetic improvement obtained with the treatment according to GAIS (Global Aesthetic Improvement Scale)[26] and the evaluation of subjects' and investigators' satisfaction with the treatment and evaluation of product safety assessed by subject and patient satisfaction questionnaire.

Safety objectives included the recording and follow-up of adverse events (AE) that have or may have a causal relationship with the investigational medical device or with the treatment methodology, recording and follow-up of serious adverse events (SAE), and recording of product deficiencies.

Photographic Methods

Standardized photographs were taken before treatment and at the follow-up visit. The photographs were taken using a smartphone under artificial light and with a uniform background. The evaluation was done by two evaluators using photographs from Day 0 and Day 7, with the Principal Investigator conducting the baseline assessment.

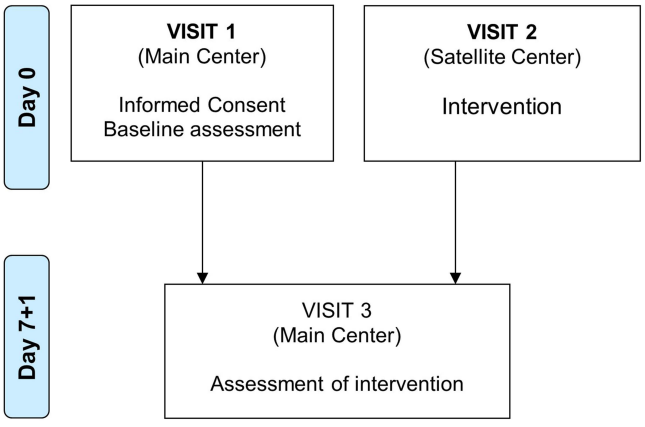

Figure 1 Outlines the visit schedule.

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Injection Technique

A topical solution (1% chlorhexidine solution) was applied to the treatment area 30 minutes before the procedure. The cream was removed, and the area sterilized with 75% ethanol. The product was injected using a microdermal papule technique (Figure 2).

Classification of Photoaging

We assessed the grade of photoaging using the established Crow's Feet Grading Scale for dynamic and static rhytids.[18] It is a 5-point photonumeric scale with the following ratings: 0 for no wrinkles, 1 for very fine wrinkles, 2 for fine wrinkles, 3 for moderate wrinkles, and 4 for severe wrinkles.[18] The evaluation is performed at rest (static) and with expression (dynamic).[18]

Evaluation of Infraorbital Dark Circles

We assessed infraorbital dark circles with a validated 10-point photonumeric scale with corresponding descriptors and images for each grade of the scale.[27] The following grades were considered: 0 for no dark circles, 1 for barely perceptible dark circles, 2 for slight dark circles, 3 for mild dark circles, 4 for mild to moderate and noticeable dark circles, 5 for moderate and obvious dark circles, 6 for moderate to pronounced dark circles, 7 for pronounced and distinct dark circles, 8 for pronounced and significant, dark circles, and 9 for extensive, severe dark discoloration.[27]

Satisfaction Questionnaire

Both the patient and the investigator completed a satisfaction questionnaire after treatment. This questionnaire assessed satisfaction regarding feelings of rehydration, elasticity, rejuvenation, luminosity, and general satisfaction.

Safety Analysis

We recorded any adverse events that occurred during the clinical investigation and assessed a potential or causal relationship with the investigational medical device or with the research methodology. The adverse events were graded according to their intensity (mild, moderate, severe) and time of onset (immediate onset - up to 24 h after procedure; early onset - 24 h to 1 week), following the Expert Consensus Recommendation Report for the treatment of complications related to the injections of soft dermal implants.[28] Furthermore, device deficiencies are also recorded.

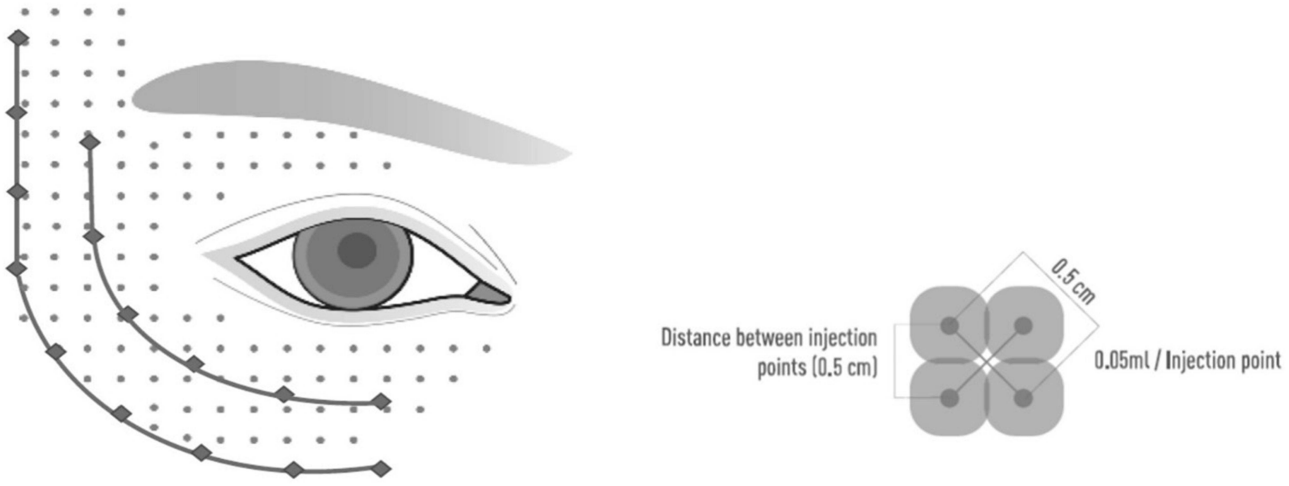

Figure 2 Schematic diagram of the application area.

Statistical Analysis

Descriptive statistical analysis was performed for quantitative biometric variables (skin hydration) and ordinal scaled data (degree of lateral canthal rhytids and infraorbital dark circles). Linear mixed-effects models (LMM) and cumulative mixed models (CLMM) were used to assess treatment effects. Significance was set at $p < 0.05$.

The sample size was calculated according to statistical factors such as assumptions, error alpha, beta error, statistical power, and variability, losses in the study and size effect.[29]

Results

Patient Population

Thirty-four (34) patients completed the study. The mean age was 53 ± 7.58 and most patients were women (82%) (n=28, 82%). The study included patients with Fitzpatrick skin phototypes II (n=12, 35%), III (n=17, 50%), and IV (n=5, 15%).

An overview of demographic data is provided in Table 1.

Hydration Efficacy

Skin hydration significantly increased from 57.17 ± 11.04 at baseline to 58.83 ± 7.36 at 7 days, with an average increase of 3% ($p < 0.05$). Improvement in skin hydration was confirmed in 71% of patients.

Evaluation of Lateral Canthal Rhytids

Dynamic Rhytids

An average reduction of 6% in the Crow's Feet Grading Scale (dynamic) was observed, which was statistically significant ($p < 0.05$), decreasing from a mean score of 2.76 ± 0.69 to 2.59 ± 0.76 at 7 days. Thirty-two percent (32%) of patients showed an improvement.

Static Rhytids

An average reduction of 4% in the crow's feet grading scale (static) was observed, with a mean score of 1.53 ± 0.68 at baseline and 1.47 ± 0.70 at 7 days. This difference was not statistically significant. Nine percent (9%) of patients showed an improvement.

Evaluation of Infraorbital Dark Circles

An average reduction of 11% in the photonumeric scale for infraorbital dark circles was observed, which was statistically significant ($p < 0.05$). The evaluation of the undereye area was rated at 3.63 ± 1.13 at baseline and decreased to 3.22 ± 1.03 at the final visit. Fifty percent (50%) of patients showed an improvement.

Table 1 Patient Demographics

	Mean	Standard Deviation (SD)	Range
Total Participants	**34**	**–**	**–**
Gender **Male** **Female**	 6 (18%) 28 (82%)	–	–
Age	53.24	7.58	33-71
Height	164.38	8.25	150-184
Weight	68.40	12.14	45-93

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Table 2 Absolute and Relative Frequencies of the GAIS Scale for PI and Subjects (n=34)

GAIS	Principal Investigator (n (%))	Patients (n (%))
Much worse	0 (0%)	0 (0%)
Worse	0 (0%)	0 (0%)
No change	11 (32%)	9 (26%)
Improved	23 (68%)	18 (53%)
Much improved	0 (0%)	7 (21%)

Global Aesthetic Improvement Scale (GAIS)

The Principal Investigator reported that 68% of patients either "improved" or "much improved", which was comparable to patients' evaluation (74% "improved" or "much improved"). The GAIS results are shown in Table 2 and Figure 3. The patients' photographs taken during the baseline visit and one week after the product application are presented in Figures 4 and 5.

Satisfaction Questionnaire

From the patients' perspective, 73% reported feeling their skin more hydrated, 71% experienced increased elasticity, 53% felt their skin appeared more rejuvenated, and 65% noticed a smoother texture. In terms of overall satisfaction, 82% of patients expressed being either satisfied or very satisfied with the treatment results. According to the investigator's assessment, 79% of patients exhibited increased skin hydration, 6% showed improved elasticity, 65% appeared more rejuvenated, and 65% had smoother skin. Overall, the investigator reported satisfactory or very satisfactory outcomes in 74% of patients.

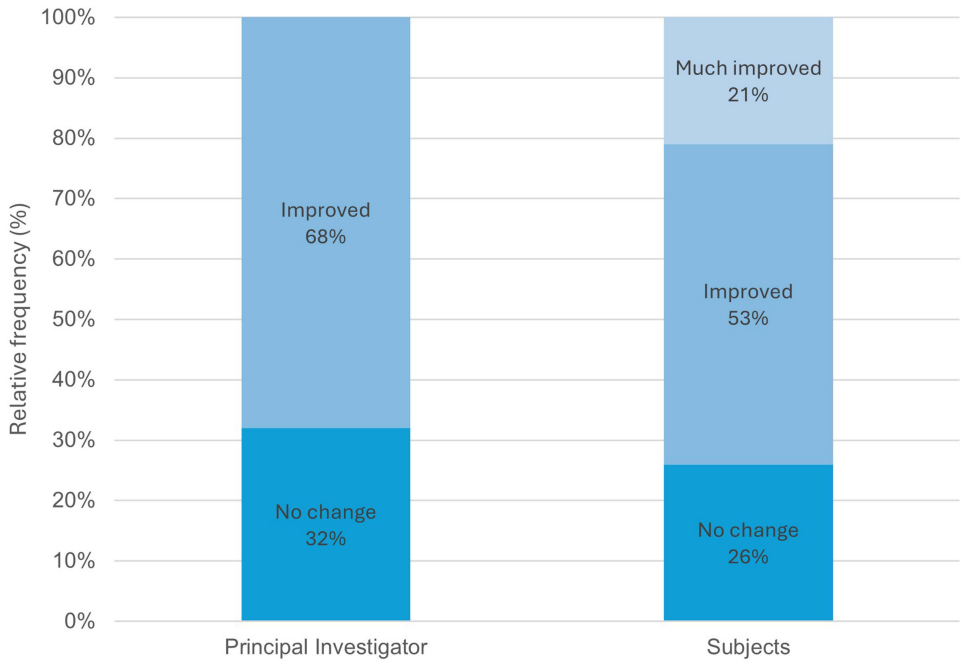

Figure 3 Bar plot with relative frequencies of the GAIS scale for the principal investigator and patients.

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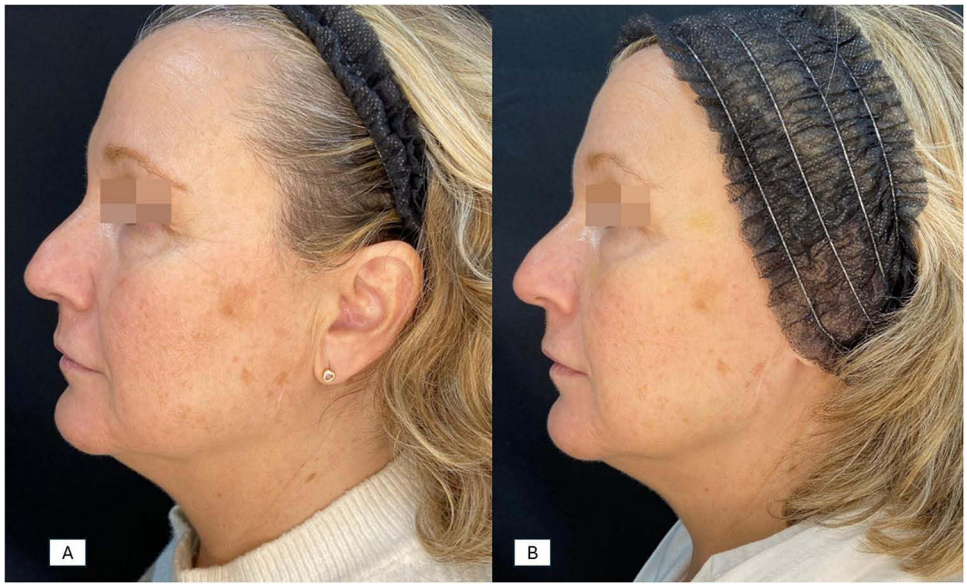

Figure 4 Patient (51-year-old female). Baseline (**A**) and post-treatment (**B**) photographs.

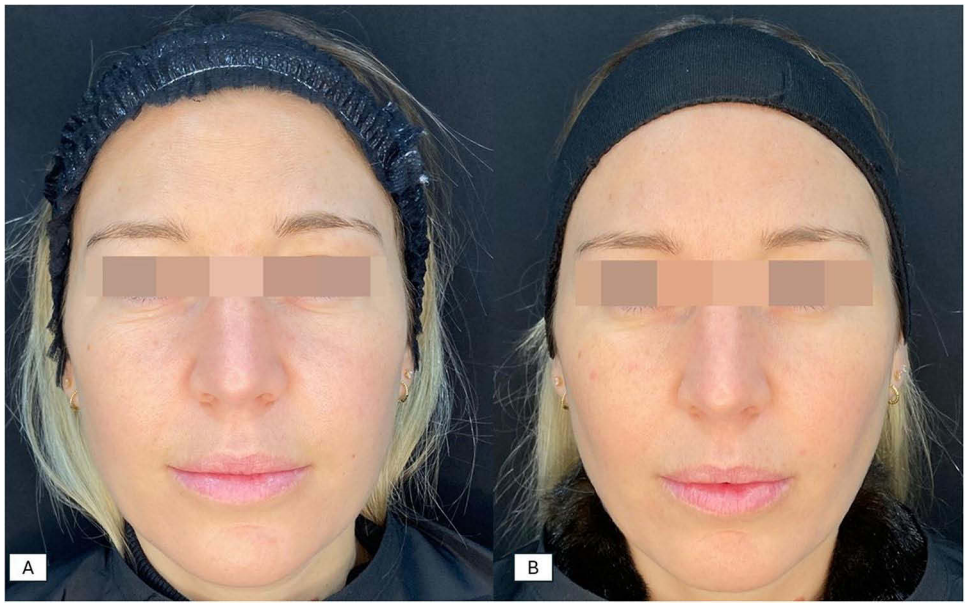

Figure 5 Patient (33-year-old female). Baseline (**A**) and post-treatment (**B**) photographs.

Safety Assessment

No serious adverse events or product deficiencies were recorded. Adverse events were mild and resolved spontaneously, with the majority not exceeding two weeks in duration. Ecchymosis was the only reported local application effect reported in the study and occurred in 44%.

Discussion

Hyaluronic Acid (HA) is a naturally occurring component of the extracellular matrix in human skin. As the skin ages—either through natural processes or accelerated by excessive UV exposure—HA levels decline, and crosslinking increases over time. HA functions by binding and retaining water molecules, which helps maintain skin hydration.[7,8] When

introduced into the skin via injection, exogenous HA acts as a biological humectant, enhancing water retention and improving skin moisture.[30]

In our study, we assessed the effect of a single session of non-crosslinked HA injections with the microdermal papule technique applied in the periorbital area 7 days after the injection. A total of 34 patients were included. The principal aim of this clinical investigation was to assess the efficacy of the non-cross-linked HA associated with a protective buffer in improving the hydration levels of skin affected by photoaging. Specifically, this study included patients with lateral canthal rhytids graded between 1 and 4 on the Crow's Feet Grading Scale. The intervention involved the administration of an investigational medical device to the facial region during a single session, followed by a monitoring period spanning up to 7 days. The chosen research protocol adhered to established standards and guidelines, drawing from a recommended and previously employed protocol within the same time frame as other post-market follow-up activities. This selection was based on the compatibility of the protocol with the study's objectives and timelines.

Externally applied HA is broken down in the skin, with the degradation rate influenced by its molecular weight and degree of cross-linking.[31] As a result, the current clinical study using non-cross-linked HA incorporated a short follow-up period of 7 days, consistent with other studies evaluating similar products.[21]

Seven days after the application of the product, a statistically significant increase in skin hydration of 3% was noted compared to baseline. An improvement in infraorbital dark circles was confirmed in 50% of patients with an average reduction of 11% in the photonumeric scale. Seventy-four percent (74%) "improved" or "much improved" according to the GAIS scale, which was in line with the investigators' evaluation (68% improvement).

Evidence from similar devices used in the same treatment area as in our study is limited. Kabakci et al treated 23 women with HA filler injections in the periorbital area with three applications in total.[32] Similar to our results, the decrease in dark circle and wrinkle scores was minor after one session, but the authors confirmed significant improvements one month after the third application.[32] Patient satisfaction also improved, although the authors did not use the GAIS for their assessment.[32] Information on safety was not provided. Pascali et al conducted a retrospective study to compare the results of HA fillers with lipo-filling in a group of 96 patients with periorbital hollowing.[33] The number of applications is not entirely clear from the manuscript, but an improvement in the Barton Grading System was noted in almost all patients treated with the HA filler, although the lipo-filling resulted in a more long-lasting effect up to one year.[33] In line with our results, there were no significant complications and no patient experienced palpable indurations.[33] The largest comparable study was published by Berguiga et al with 151 patients and a follow-up of three weeks.[34] The HA filler was again applied to the periorbital region in a single session with a potential touch-up injection at one month that was requested by 18%.[34] Safety results were comparable with our observations since all events occurred immediately after the injection and were related to well-known side effects, such as transient bruising, swelling, and redness.[34] GAIS results according to the patients were very favorable and slightly higher than our results (97% with versus 74% reported as "much improved" or "improved").[34] However, these results could be biased by the retrospective nature of the study.

Similar results with regards to increased skin hydration were confirmed in other studies with non-crossed-linked HA with high patient and investigator satisfaction.[21,23] Duteil et al used a Corneometer® to assess the hydration status after three full-face applications of non-cross-linked HA.[23] They obtained a 35% increase 10 days after the third application.[23] Measurements after the first injection were not reported, which limits the comparison with our results.[23] In contrast, the injection on non-cross-linked HA in the periorbital area did not cause a statistically significant increase in hydration in the periorbital area despite three applications at intervals of three weeks.[35]

Corneometric assessments immediately after application were reported by Lee et al who applied a microstructure patch with cross-linked HA. Hydration in the periorbital area increased by about 7% and 9% at 3 and 6 days and thus slightly higher but comparable to our results.[36] The noted improvements in our study were significant but modest. Other studies showed that the combination of HA with other treatments such as platelet-rich plasma can further improve treatment results.[37] However, the investigational medical device in our study was applied as a standalone treatment and future studies would be needed to evaluate the effect several repetitive treatments (the whole treatment course).

The results from a recent publication from Bezpalko and Filipsky, in which skin quality was assessed after injection of two different non-crosslinked HA-based fillers revealed that signs of skin hydration persisted even 3 weeks after injection of both HA fillers, although no signs of remaining injected HA were detectable by ultrasound.[30]

Several other treatment options exist, with chemical peelings being another frequently applied skin rejuvenation technique.[38] These procedures involve the controlled application of a chemical wounding agent to promote exfoliation followed by regeneration of healthier skin.[39–43] Beyond improving the visible appearance of the skin, chemical peeling facilitates histologic repair by reducing epidermal atrophy and stimulating new subepidermal collagen formation.[12,41,44] Although considered safe and predictable in terms of efficacy, TCA peels require a healing period of approximately one week, during which visible desquamation may limit patient acceptability.[38]

Common side effects of dermal filler injections include redness, swelling, and potential infection at the injection site.[24,25] Although rare, more serious complications can occur, such as vascular occlusion, which may result in skin necrosis, blindness, or stroke.[25] The choice of application instruments, as well as the injection pressure and volume, can influence the risk of adverse events.[25] Therefore, it is essential for aesthetic practitioners to possess a thorough knowledge of facial anatomy and injection techniques to reduce the likelihood of these serious complications.[25]

Consistent with findings from systematic reviews[24,25] and clinical studies using non-cross-linked HA,[21,22,37] the safety evaluation of the study cohort revealed only mild adverse events during the follow-up period, all of which resolved without additional treatment.

Limitations

Our investigation inherits certain limitations. The follow-up time was relatively short with an assessment 7 days after a single injection. Although the main effects and also side effects are usually obtained within this timeframe, long-term effects were not evaluated. Additionally, the non-blinded design and a lack of a comparator group can introduce bias. Lastly, the relatively small sample size needs to be considered.

Conclusions

The primary objective of this clinical investigation was to assess the efficacy of non-cross-linked HA associated with a protective buffer in improving skin hydration levels of the periorbital area in patients affected by photoaging. From the results presented, we saw a slight but statistically significant improvement in photoaging grading as assessed by the Crow's Feet Grading Scale and a statistically significant improvement in skin hydration. Overall, patient satisfaction was considered good. The intervention can be regarded as safe, with no serious adverse events or device deficiencies reported.

Further investigation in randomized controlled trials in a broader range of patients is needed to assess efficacy and performance and confirm the long-term safety of injectable non-crosslinked HA to remove signs of photoaging by increasing skin hydration.

Data Sharing Statement

The authors do not intend to share individual deidentified participant data.

Upon request, the following documents will be made available: synopsis of the clinical study report, statistical analysis. No further study documents will be made available.

The data will be made accessible upon request to the corresponding author for a 2-years period.

Ethics Approval

The study was approved by Regional Research Ethics Committee of the Community of Madrid on July 4th, 2022. Prior to commencement, the study was submitted to the registry of the AEMPS (Spanish Agency of Medicines and Medical Devices) through NEOPS (Application for Electronic Notification of Clinical Investigations with CE-marked medical devices for approved indications with variations from standard clinical practice). The application number was 22-0059, and it was noted on 02/09/2022.

All patients signed the Informed Consent Form prior to the start of any study-related procedures.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

Dr Philippe Deprez is a former CEO of Skin Tech Pharma Group, S.L.U. Dr Evgeniya Ranneva is a former COO of Skin Tech Pharma Group, S.L.U. Oxana Doroshenko and Albina Mustafina are affiliated with Skin Tech Pharma Group, S.L.U. The authors declare that they have no other competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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