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RESEARCH ARTICLE

HYALURONIC ACID BEYOND SKIN REJUVENATION: THE INTERSECTION BETWEEN BEAUTY AND SAFETY IN COMPLIANCE WITH THE NEW EU MEDICAL DEVICES REGULATION

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Abstract

Hyaluronic acid-based mesotherapy has become a highly popular and valuable option for facial rejuvenation, with a renowned efficacy and safety profile.The new European Regulation (EU) 2017/745 on medical devices remarks the need for post-market clinical follow-up to guarantee safety and efficacy during the entire life cycle of medical devices. In line with the new regulation, we aimed to further evaluate the clinical performance and safety of hyaluronic acid-based mesotherapy within routine practice in a period of 9 weeks. The present work is anobservational, prospective, open and non-controlled study in a cohort of patients treated with hyaluronic acid-based mesotherapy for facial aging. Patients between 30 and 75 years old, treated with hyaluronic acid 1% injections for facial rejuvenation, were included. Point-by-point and epidermal administration techniques were usedin three visits (initial, 3 weeks and 6 weeks). The outcomes were measured using GAIS for efficacy and VAS for patient' satisfaction. A total of 25 patients underwent hyaluronic acid mesotherapy in the face or neck, and were followed up for 9 weeks. Throughout the study, a significant improvement ($p < 0.05$) in skin appearance and hydration was observed in both groups between first and last visit. No significant differences were observed between the two groups. All participants showed increased skin hydration and/or reduced fine lines. In conclusion, hyaluronic acid-based mesotherapy is effective for facial and neck skin boosting, with an excellent safety profile, highlighting the potential of linear hyaluronic acid as a non-surgical solution for skin rejuvenation.

Introduction:-

Skin aging is a complex biological process that involves biochemical and structural changes that can be physically and emotionally challenging for individuals seeking to maintain a youthful appearance. This process occurs naturally due to intrinsic factors, such as oxidative stress due to the accumulation of reactive oxygen species (ROS), senescence of fibroblasts, imbalance in collagen production and degradation, and fragmentation of elastin belonging to the dermal elastic fiber network.(Shin, Lee, Rho, & Park, 2023) Moreover, skin aging can be enhanced or accelerated due to external factors such as ultraviolet (UV) rays, pollution and smoking.(Burke, 2020; Parrado et al., 2019) The progress of these biochemical processes gives rise to the gradual development of signs of facial aging

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such as fine lines, wrinkles, skin dehydration, spots, depigmentation, loss of volume and elasticity, and changes in skin texture.(Swift, Liew, Weinkle, Garcia, & Silberberg, 2021) As a result, facial skin rejuvenation has become a pivotal objective of aesthetic medicine, promoting the development of new techniques designed to prevent and counteract the effects of skin aging. Plastic surgery has traditionally held a central role in the pursuit of a youthful appearance, but surgical interventions often carry inherent risks, long recovery, and eventual complications. As demand for safer and minimally invasive techniques for facial rejuvenation has increased, nonsurgical procedures such as dermal fillers and mesotherapy have become valuable alternatives.(Iranmanesh, Khalili, Mohammadi, Amiri, &Aflatoonian, 2022; Li et al., 2022; Trinh Sarah E., Gupta Amar, 2021) One of the key components responsible of its effectiveness is hyaluronic acid.

Hyaluronic acid (HA), an essential component of the extracellular matrix, is a naturally occurring glycosaminoglycan that plays a key role in maintaining skin hydration, elasticity, and structural integrity.(Papakonstantinou, Roth, &Karakiulakis, 2012; Šínová, Pavlík, Ondrej, Velebný, &Nešporová, 2022; Wu, Kam, & Bloom, 2022) Its attributes include the great ability to attract and retain water, contributing to skin hydration and volume restoration,(Wu et al., 2022) and boosting collagen production by fibroblast stimulation.(Deglesne PA, Arroyo R, Ranneva E, & Deprez P, 2016) The application of injectable HA in facial rejuvenation has become a prominent and well-established technique that offers non-surgical solutions to effectively combat skin aging, with numerous studies demonstrating its efficacy.(Baspeyras et al., 2013; Bezpalko L &Filipskiy A, 2023; Duteil L et al., 2023; Fanian et al., 2023; Tedeschi, Lacarrubba, & Micali, 2015) Cross-linked HA, whose degradation is slower, is mainly used as a dermal filler,(Fundarò, Salti, Malgapo, & Innocenti, 2022; Wu et al., 2022) while linear or non-cross-linked HA, is used in techniques such as mesotherapy or microinjections to obtain a more natural effect improving the appearance and texture of the skin.(Iranmanesh et al., 2022)

The new European Medical Devices Regulation (EU) 2017/745(Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on Medical Devices, Amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and Repealing Council Directives 90/385/EEC and 93/42/EEC, 2017) points out, as a noteworthy novelty, the need to accomplish clinical investigations once the product is on the market, as a post-market clinical follow-up plan, and not be exclusively limited to conducting investigations until product registration. In aim to complying with this regulation, we designed a post-marketing study to further evaluate the clinical performance and safety of a HA-based injectable product (AcHyal®, Meiji Pharma Spain) in facial rejuvenation under real clinical conditions.

Patients and Methods:-

Ethics

This study was authorized by the Ethics Review Board of the Hospital Universitario Puerta de Hierro (Madrid, Spain) (date of approval 07/11/2022). Participants gave their informed consent for the intervention. They also gave a specific consent to be photographed and for the subsequent use of the photos in scientific publications. The photographs taken during the study were handled exclusively by the researchers in order to evaluate the results according to the GAIS scale. The photographs were edited and cropped so that only the treated areas were shown and did not allow the identification of the patients. The original ones were deleted, and no photos were included in the Data Collection Forms.

Study Design

Observational, prospective, open and non-controlled, in a cohort of patients treated with HA for the treatment of signs of facial aging. The treatment consisted of the infiltration of 2.5-5 mL, per session, of HA 1% (AcHyal®, Meiji Pharma Spain) on face and/or neck. This HAis obtained throughbacterial fermentation (*Streptococcus zooepidemicus*), andhas linear structure and an average molecular weight of 1000 kDa. The possible administration techniques to be used were point-by-point, nappage, and epidermal. On each case, the appropriate technique, volume and depth were established at the criteria of the investigator. At a first appointment, patients were selected and the first administration of HA was performed. Follow-up visits were performed at 3, 6 and 9 weeks. Additional HA injections were administered at 3- and 6-weeks visits. At every visit, investigator'sefficacy assessmentand patient grade of satisfactionwere recorded, as well as any adverse events that could appear. Photographs were taken before and immediately after the infiltration (at least one photograph from the front and another with a rotation of 45°).

Patients

The inclusion criteria were male or female sex, age between 30 and 75 years old, indication for the aesthetic intervention due to dehydration, and lack of luminosity and firmness, the ability to understand and comply with the study procedures, and having given the informed consent. Candidates who met any of the following characteristics were excluded: previous surgery or permanent filler injection in the area to be treated, known or suspected hypersensitivity to HA, history of keloid formation, infection, unhealed wound or active inflammatory process at the injection site, any active acute or chronic infection requiring parenteral antimicrobial therapy, immunocompromised patients or patients receiving systemic immunosuppressive therapy, any skin condition or disorder, severe central nervous system disorder, diabetes mellitus or uncontrolled systemic diseases, any pathology which, in the opinion of the investigator, may interfere with administration or evaluation, patients awaiting maxillofacial surgery, pregnant or lactating women, women of childbearing potential who do not use effective contraceptive methods, previous participation in this protocol. During the study, participants were not allowed to use creams or treatments that might interfere with the evaluation of efficacy.

Outcome Measures

Efficacy of the treatment was assessed using the investigator Global Aesthetic Improvement Scale (GAIS),(Savoia, Accardo, Vannini, Di Pasquale, & Baldi, 2014) a five-point Likert scale that ranges from "exceptional improvement" (score = 5) to "worse" (score = 1) (Table 1), and the Visual Analogue Scale (VAS)(Freyd, 1923) for the patient. The VAS consists of a scale ranging from 0 to 100, where higher values are associated with greater satisfaction.

Table 1:- Global Aesthetic Improvement Scale (GAIS).

Score	Description
5 = Exceptional improvement	Excellent corrective result.
4 = Significant improvement	Noticeable improvement in appearance but not optimal.
3= Improvement	Improvement of the appearance, it is better compared to the initial state but a touch up is recommended.
2 = Unvarying	The appearance remains substantially the same compared to the original state.
1 = Worse	The appearance has worsened compared to the original state.

Safety Evaluation

Adverse events and physical examination were considered as safety variables. The following data related to adverse events were registered: duration, severity, relationship to study product, treatment, measures taken in relation to the test product, and outcome.The relationship of the adverse event to the product was rated according to the Karch and Lasagna algorithm.(Karch & Lasagna, 1977)

Statistics

For the descriptive phase, the mean and standard deviation were used in the case of quantitative variables. To demonstrate the normality of the quantitative variables, the Kolmogorov-Smirnov test was used. For the qualitative variables, percentages were used. In the case of inferential statistics, the t test or Mann Whitney were used to make comparisons between independent groups, for paired samples the t test was used to make comparisons between independent groups, and for pre-post comparisons Wilcoxon was used.

Results:-

A total of 25 patients were included in the study between November 18th 2022 and March 3rd 2023. The mean age was 58.7 years old (SD 7.0), with a minimum of 46 years old and a maximum of 71 years old. In 40% of cases, patients were taking concomitant medication (more than one medication may correspond to the same patient): antidepressants (16%), levothyroxine (12%), benzodiazepines (8%), proton pump inhibitors (8%), statins (8%), losartan (4%), bilastine (4%), flavonoids (4%) and acetyl salicylic acid (4%), and an 88% of patients had been vaccinated against Covid-19.

Treatments were performed on the face or neck. The injection techniques used, the injection sites in the case of the face, the use of local anaesthesia, and the injected volume are shown in Table 2. The most commonly used injection

technique was point-by-point, in the case of the face the most treated area were the cheekbones, and the injected volume ranged from 2.5mL at the first visit to between 2.5 and 5 mL at subsequent visits.

Table 2:- Summary of the interventions.

		Face			Neck		
Visit		**V1**	**V2**	**V3**	**V1**	**V2**	**V3**
Treated patients		17 (68.0%)	17 (68.0%)	17 (68.0%)	8 (32.0%)	8 (32.0%)	8 (32.0%)
Technique	**Point-by-point**	15 (88.2%)	15 (88.2%)	16 (94.1%)	8 (100%)	8 (100%)	8 (100%)
	Epidermal	2 (11.8%)	2 (11.8%)	1 (5.9%)	-	-	-
Injection site*	**Cheekbones**	16 (94.1%)	16 (94.1%)	16 (94.1%)	-	-	-
	Nasolabial fold	9 (52.9%)	9 (52.9%)	9 (52.9%)	-	-	-
	Perioral fold	6 (35.5%)	3 (17.6%)	6 (35.5%)	-	-	-
	Neck wrinkles	-	-	-	8 (100%)	8 (100%)	8 (100%)
	Marionette lines	8 (47.1%)	12 (70.6%)	14 (82.4%)	-	-	-
Local anesthesia		5 (29.4%)	3 (17.6%)	3 (17.6%)	8 (100%)	6 (75.0%)	6 (75.0%)
Injected volume (mL), mean, (dt)		2.5 (0.0)	3.38 (1.23)	3.53 (1.27)	2.5 (0.0)	4.06 (1.29)	4.06 (1.29)

* More than one injection site may correspond to the same patient.

The assessment of efficacy was carried outby the researcher with the GAIS scale and the patients' satisfaction with the VAS scale (Table 3), and a progressive increase in patients and researcher satisfaction in both neck and face groups was observed (Figures 1 and 2). When compared with the first visit,the analysis revealed significant differences with the subsequent ones, indicating a clear trend to improvement (Table 4). In the facial treatment group, the GAIS scores exhibited a statistically significant differences in all follow up visits (V2, V3, V4) when compared to the initial visit (V1).

Table 3:- Efficacy results.

Group	**Variable**	**Visit**			
		V1	**V2**	**V3**	**V4**
Face	GAIS, mean (SD)	3.53 (0.8)	3.88 (0.60)	4.06 (0.66)	4.29 (0.59)
	VAS, mean (SD)	82.5 (11.6)	81.1 (11.5)	86.1 (7.0)	87.7 (4.4)
Neck	GAIS, mean (SD)	3.32 (0.75)	3.50 (0.54)	4.13 (0.35)	4.25 (0.71)
	VAS, mean (SD)	67.5 (11.7)	77.5 (5.3)	83.1 (4.6)	88.1 (3.7)

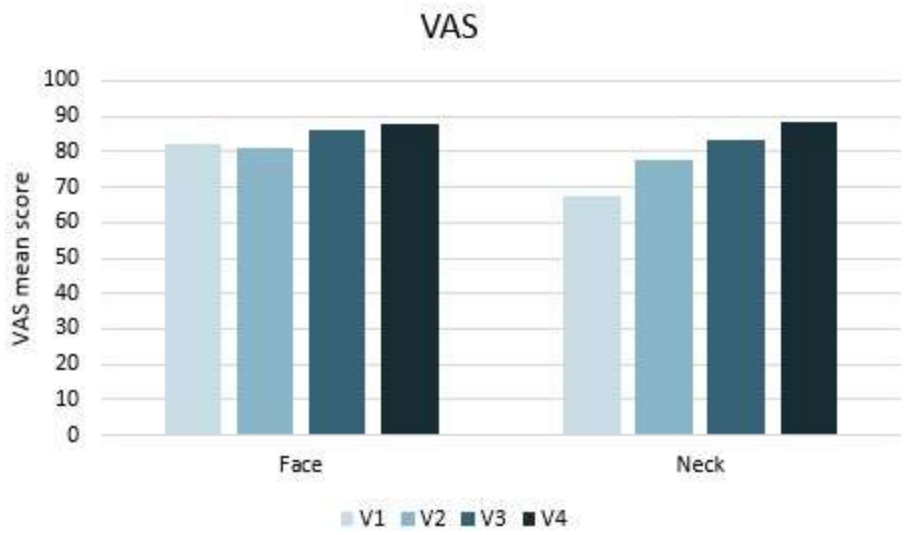

Figure 1:- Evolution of VAS mean score throughout the study. Higher values indicate higher patient satisfaction. The visits are indicated as V1-V4.

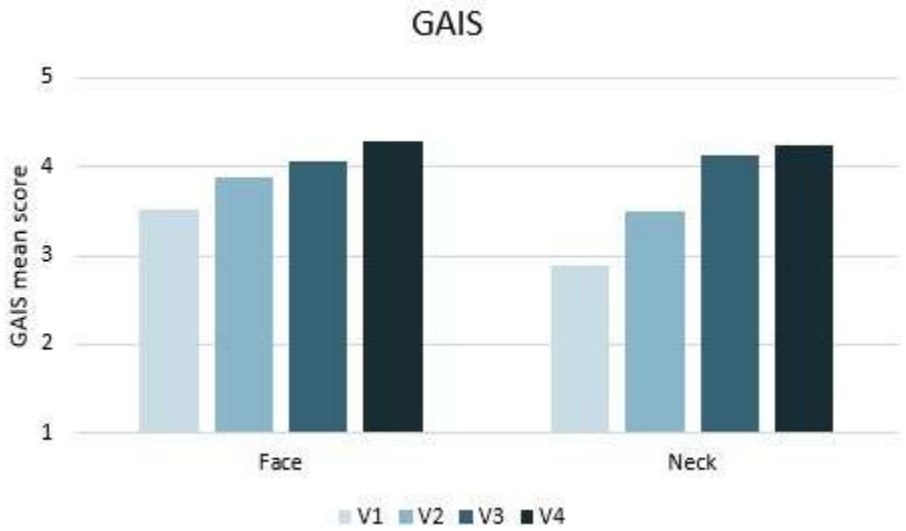

Figure 2:- Evolution of GAIS mean values throughout the study. Higher values indicate higher investigator satisfaction. The visits are indicated as V1-V4. .

Table 4:- Pre- and Post-data comparison for paired samples.

Group	Variable	Differences		
		V1-V2	V1-V3	V1-V4
Face	GAIS, mean (SD)	-0.353 (0.996)	-0.529 (0.800) *	-0.765 (0.916) *
	VAS, mean (SD)	1.412 (14.689)	-3.588 (8.704)	-5.176 (10.501)
Neck	GAIS, mean (SD)	-0.625 (0.518) *	-1.250 (0.707) *	-1.375 (0.916) *
	VAS, mean (SD)	-10.000 (12.247)	-15.625 (13.479) *	-20.625 (12.660) *

* Statistically significant ($p < 0.05$).

However, the VAS scores, while showing substantial improvement, narrowly missed the threshold for statistical significance, being almost significant. In the neck treatment group, the differences between visits 3 and 4 relative to

the initial visit were found to be statistically significant for both GAIS and VAS scores. Additionally, visit 2 demonstrated a statistically significant improvement in GAIS when compared to the initial visit, yet the VAS scores did not exhibit a significant difference. The improvement assessment by patients (VAS) on the first visit it is significantly greater in patients treated in the face than in those treated in the neck, but not on the following visits. The GAIS showed no significant differences between both groups, and showed a clear overall trend towards significant improvement and exceptional improvement throughout the study (Figure 3).

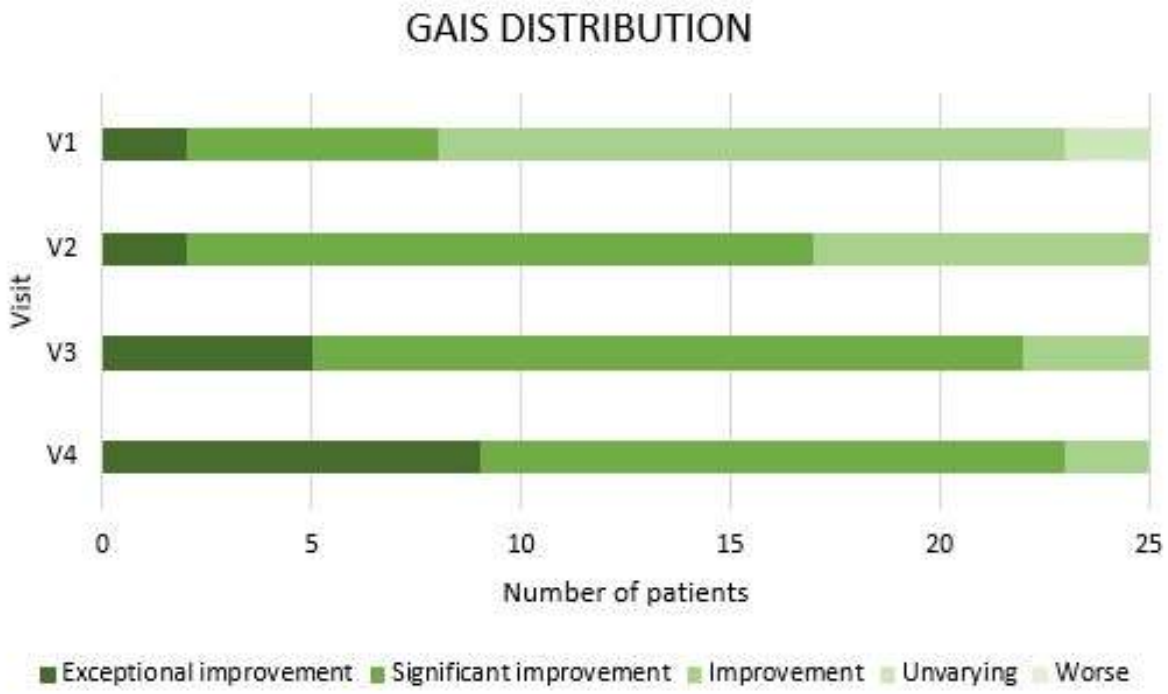

Figure 3:- GAIS distribution throughout the study. Higher values indicate higher improvement. The visits are indicated as V1-V4, respectively.

The results demonstrated a significant improvement in facial skin quality in both groups due to the HA mesotherapy. Participants exhibited enhanced skin hydration and reduced fine lines, as can be observed in Figures 4 and 5 for face and neck, respectively. Regarding the safety profile, no adverse events related to the use of HAwere observed.

Figure 4:- Skin improvement in a patient treated on the face using HA-based mesotherapy. On the left is shown the skin at the initial visit, on the right is shown the skin at the final visit.

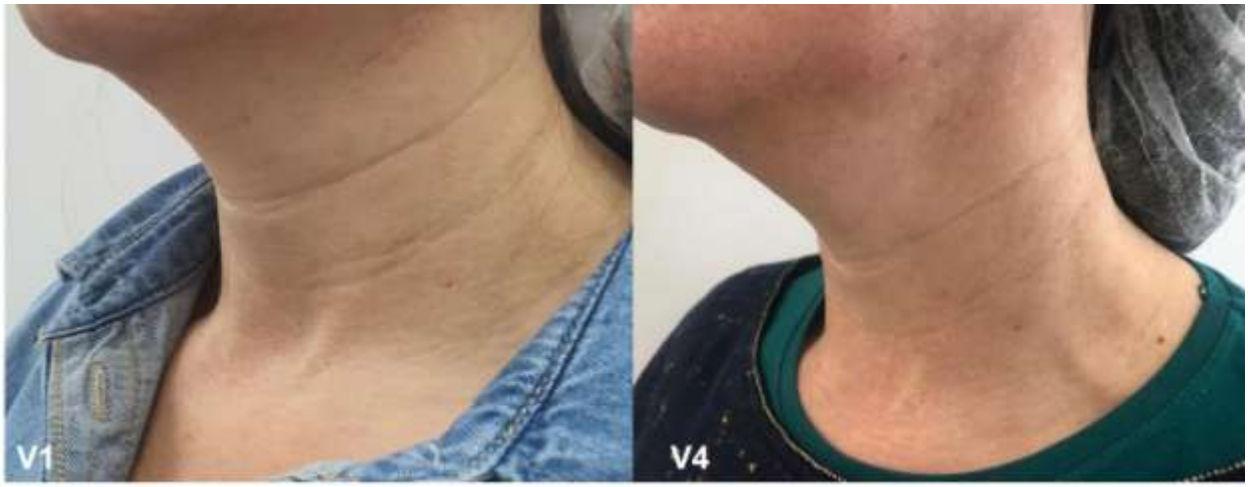

Figure 5:- Skin improvement in a patient treated on the neck using HA-based mesotherapy. On the left is shown the skin at the initial visit, on the right is shown the skin at the final visit.

Discussion:-

The utilization of HA in mesotherapy has become increasingly common in the field of aesthetic medicine due to its well-documented safety profile and multiple benefits.(Ghatge & Ghatge, 2023; Rohrich, Bartlett, & Dayan, 2019) The synthesis of collagen fibers in response to HA injections contributes to the restoration of youthful skin characteristics. Hyaluronic acid's ability to stimulate collagen production,(Cabral et al., 2020) an essential protein for skin elasticity and firmness, further enhances its appeal as a mesotherapy agent. The findings of our study align with previous researches indicating the positive impact of HA in skin rejuvenation.(Bezpalko L &Filipskiy A, 2023; Duteil L et al., 2023; Fanian et al., 2023; Tedeschi et al., 2015) A significant difference in patients and investigator satisfaction was observed between the final evaluation and the initial visit, demonstrating the efficacy of linear HA mesotherapy in the treatment of the signs of facial aging. In addition, no significant differences were seen between patients treated in the neck and patients treated in the face, highlighting a similar efficacy of the treatment in both areas. The increase in improvement as the number of injections increases suggests a carry-over effect that indicates a potential long-lasting benefit of HA mesotherapy. This effect may be attributed to the ability of HA to stimulate collagen production, improve tissue hydration, and maintain skin elasticity over time. In the course of this study, no adverse events associated with the administration of HA were detected, underscoring its excellent safety profile. It is worth noting that previous research has reported adverse events related to the use of cross-linked HA in Covid-19 vaccinated patients,(Beamish, Bogoch, & Carr, 2022) but in this case no such events occurred, highlighting the distinct safety advantages of linear HA. This study has made it possible to evaluate the efficacy and safety of aesthetic injections of linear HA in routine clinical practice. It is important to note that while the results are promising, further research is warranted to elucidate the exact mechanism underlying the carry-over effect and to determine the optimal treatment protocol for sustained benefits, including studies with a larger number of patients and over a longer period.

The implementation of Regulation (EU) 2017/745(Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on Medical Devices, Amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and Repealing Council Directives 90/385/EEC and 93/42/EEC, 2017) on medical devices has brought about a change in clinical investigations with medical devices and their post-market surveillance, as this Regulation has a strong focus on addressing their safety and efficacy throughout their life cycle via proactive clinical follow-up. The Regulation's aim is to reinforce patient safety, promote continuous product improvement and provide a rapid response to emerging safety risks by establishing rigorous post-market surveillance obligations. In light of this, our study highlights the importance of complying with the new regulation and demonstrates its relevance as a vital tool to enhance clinical decision making.

Our clinical investigation provides compelling evidence of the efficacy of HA-based mesotherapy with a linear HA for facial and neck skin boosting, with the added benefit of an observed carry-over effect and an excellent safety profile. These findings offer valuable insights for clinicians and researchers in the field of aesthetic medicine, highlighting the potential of HA as a non-surgical solution for skin rejuvenation.

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Disclosure of interest:
P. Coronel is employed by Meiji Pharma Spain. The other authors report no conflict of interest.

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