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Bioremodeling of the Forehead and Inferior Temples using Hybrid Cooperative Complexes of High and Low Molecular Weight Hyaluronans (Profhilo®)

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Abstract

Background: Hybrid cooperative complexes (HCCs) of high- and low-molecular-weight hyaluronans (Profhilo®) are commercially available to treat skin laxity. Aims: In a retrospective case series, effectiveness and safety of HCCs to regenerate skin in the upper facial region were investigated. Patients/Methods: On Days 0 and 30, 1 mL of the product was injected into each side of the inferior temporal region (2 mL in total), then 1 mL was injected into each side of the forehead (2 mL in total) via a cannula and fanning technique. Photography/video recordings were assessed on Days 0, 90, and 150. Visual analogue scale (VAS) pain questionnaires were assessed after each treatment session and the day after. Participants also completed a Global Aesthetic Improvement Scale (GAIS) questionnaire on Days 90 and 150. Adverse events were monitored throughout treatment. Results: For ten patients aged 41-71 years, photography revealed improved forehead lines, static/dynamic wrinkles, eyebrow ptosis, skin firmness and brightness, with positive impact on the frontalis muscle contraction post-treatment. Upper facial region treatment also improved middle/lower facial regions in some patients. On Day 150, 90% had "much improved" treated areas, 60% had "improved" skin brightness, 50% had "improved" skin firmness and 60% of patients had "much improved" skin appearance, according to GAIS scores. Post-treatment, the VAS pain score was 1 for 60.0% of patients. All participants indicated they would recommend this treatment, and no unexpected/serious adverse events occurred. Conclusions: HCCs of high- and low-molecular-weight hyaluronans (Profhilo®) are safe and effective for forehead and temple skin rejuvenation.

Keywords: Skin regeneration; Forehead; Temples; Face; Hybrid cooperative complexes; Profhilo®; Case series.

Introduction

During ageing, one of the first manifestations of facial wrinkles is horizontal forehead lines [1]. In a study of 200 men and women 20-70 years of age, the first visible wrinkles observed were periorbital lines in women and forehead lines in men [2]. An online survey of 603 women aged 30-65 years who were considering aesthetic treatment revealed that women aged <45 years were more likely to treat the skin of their upper face region first [3].

To achieve consistent results when treating upper face using facial injectable, it is important to understand its anatomy [4]. The skin and superficial (subdermal) fatty layer are continuous with the layers of scalp.5 However, the galea aponeurotica, divides into two very thin laminae that surround the superficial temporal artery on its trajectory towards the forehead (together known as the 'superficial temporal fascia') [5]. In the scalp, loose areolar tissue forms a separate fascia in its superficial aspect, known in the temple as the 'innominate fascia', which overlies the loose

areolar tissue of the temple and does not extend caudal to the inferior temporal septum.5 The deep fat layer of the temple is located caudal to the inferior temporal septum, which is supported by the underlying very thin layer of innominate fascia and loose connective tissue [5].

Soft tissue fillers can be used to treat temporal hollowing via three planes of injection: supraperiosteal (needle); interfascial (22G–25G cannula); and subcutaneous (22G–25G cannula). Forehead lines can also be treated with dermal fillers [6]. Hyaluronic acid-based fillers are the most popular, minimally-invasive aesthetic treatment, and their use over time has increased globally [7-9]. Commercially available hyaluronic acids have different molecular weights, ranging from 50 kDa (low molecular-weight) to ≤2 million kDa (high molecular weight), different concentration and technology [10,11].

A product based on stable hybrid cooperative complexes (HCCs) of high- and low-molecular-weight hyaluronans (Profhilo®) is produced using NAHYCO® Hybrid Technology (an innovative thermal process without the use of chemical reagents) [12]. This product comprises 32 mg of high molecular weight hyaluronic acid (1100–1400 kDa) plus 32 mg of low molecular weight hyaluronic acid (80-100 kDa) in an injectable concentration (64 mg in 2 mL) [10]. Furthermore, it has high biocompatibility and low viscosity to enable optimal product diffusion at the tissue level for target facial contour remodelling [12]. Post-marketing experience after three years of use of this product on >40,000 patients indicated that Profhilo® was safe and well-tolerated [12].

Profhilo® can be injected using the Bio Aesthetic Points (BAP) technique, which identifies five injection points on each side of the face in the malar and sub-malar areas [13]. Compared with a standard bio stimulation protocol, the advantages of the BAP technique include fewer injection points, a reduced possibility of adverse device events (bruises), and fewer treatment sessions [13].

The retrospective case series objective was to investigate the effectiveness and safety of Profhilo®, injected into the forehead and temples via a new technique using a cannula for skin regeneration in a clinic setting.

Materials and Methods

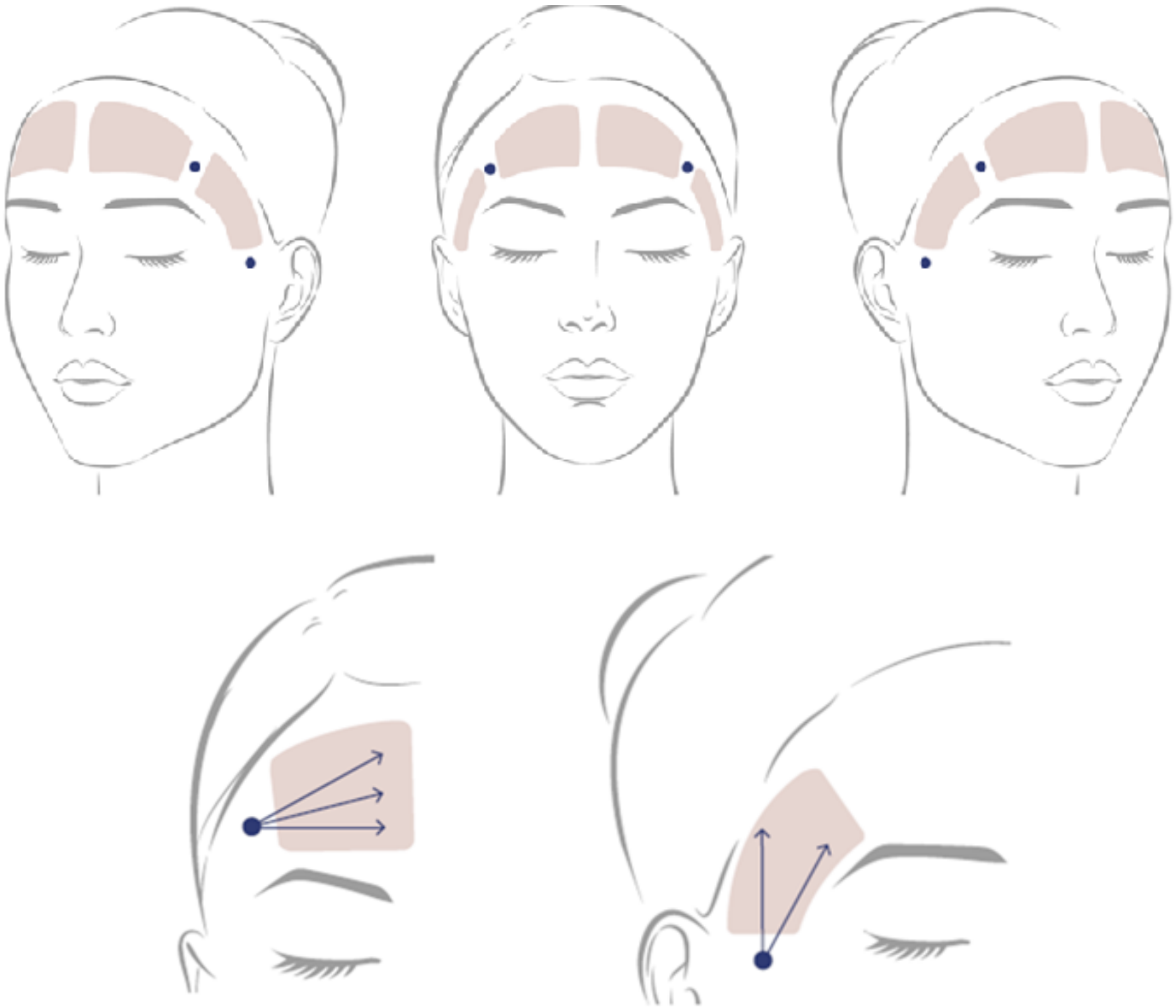
Eligibility criteria

Subjects that had undergone any facial aesthetic procedure during the last twelve months, had any skin condition in the treatment target areas of the face, or had a known allergy to hyaluronic acid were excluded from the cohort. Pregnant or breastfeeding women were also not included in this case series. Patients provided informed consent to participate in this case series and to use their images for scientific research.

Injection procedure

After using isopropyl alcohol to cleanse the skin of the face, a local anesthetic solution combining lidocaine (90% of the solution) with sodium bicarbonate (10% of the solution) has been injected in all patients prior to the treatment with Profhilo®. Specifically, 0.1 mL of the solution was injected into each of the two entry points; 0.15 mL of the solution was placed in two different points on each temple, and the same amount was injected into three different points in each side of the forehead. The points are strategically distributed in the path of the cannula to minimize discomfort. (**Video 1**).

The product was injected into the superficial subcutaneous plane of the forehead and temple regions, as close as possible to the dermis, using a 22Gx50mm cannula. The treatment was injected into forehead and temple regions using the cannula via a fanning technique14 (i.e., 1 mL for each side of the forehead and 1 mL for each side of the inferior temporal region, a total of 2 mL for each side), as shown in **Figure 1**.



After injecting a lidocaine solution in the entry points and areas of treatment, as described above, the product was placed in the superficial subcutaneous plane, as close as possible to the dermis, using a 22Gx50mm cannula. Treatment with the cannula was performed using the fanning technique (1ml for each side of the forehead; 1 mL for each side of the temporal regions). Entry points for the treatment of the forehead were made at the lateral forehead. Entry points for the inferior temporal region (area not covered by hair) were made at the lower temple area, at the zygomatic arch.

Figure 1: Treated areas of the face and the injection procedure.

Entry points for the forehead were identified at the lateral forehead to avoid intravascular injection of the supraorbital artery. Entry points for the inferior temporal region were identified at the lower temple area, at the zygomatic arch. Injections with HCC (Profhilo®) were assessed using an ultrasound scan (Versana Premier, GE Healthcare, and Chicago, Illinois, USA). During the injection procedure, an ultrasound scan was used to verify that the cannula was correctly positioned in the superficial subcutaneous layer (**Video 2**). An ultrasound scan was also used to assess product diffusion immediately after the injection.

The treatment on both forehead and inferior temporal region has been performed on Day 0 and 30 days after.

Assessments

2D-camera photographs of the patients were taken from the frontal view (in a standing position), oblique view (at a 45° angle), and the profile view on Day 0 (before the first injection), Day 90 and Day 150 (follow-up visits). Images were taken of patients with their face at rest, at maximum eyebrow elevation, maximum fronto-glabellar contraction, and whilst smiling.VECTRA M3 3D facial imaging system (Canfield Scientific, Parsippany, NJ, USA) was also used to assess the results. Videos were also recorded on Day 0, Day 90, and Day 150 to assess patients from the frontal view in a standing position, the oblique view (at a 45° angle), and whilst performing the same set of facial expressions and movements as described above.

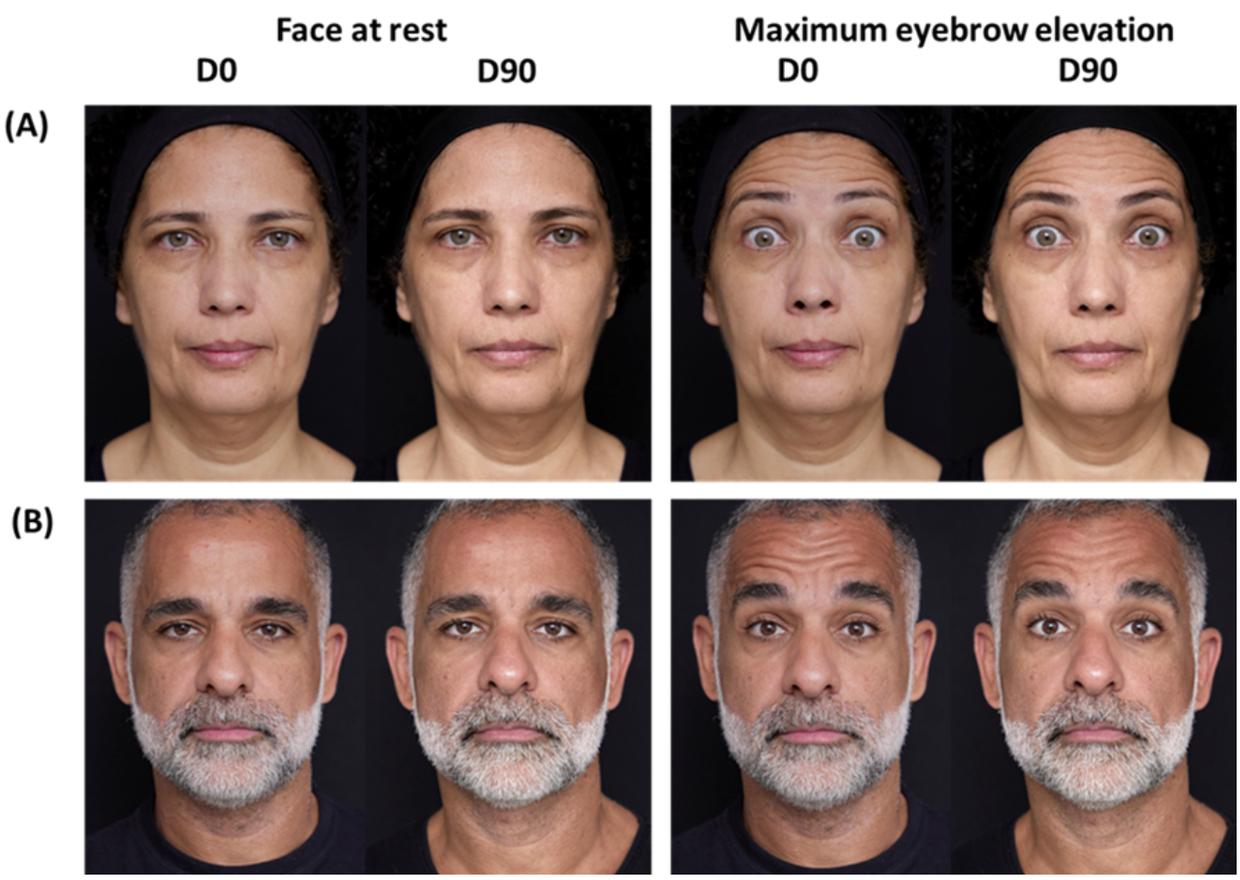
Participants also completed two patient satisfaction questionnaires, the Global Aesthetic Improvement Scale (GAIS; on Day 90 and Day 150 [follow-up visits]) and visual analogue scale (VAS) for pain (recorded immediately after treatment and the day after the treatment). Any adverse events after treatment were also recorded.

Results

Clinical assessment from images taken before and after treatment

Ten participants (seven women and three men), 41-71 years of age, were included in the retrospective case series, of whom eight (80.0%) were white and two (20.0%) were black (**Table 1**).

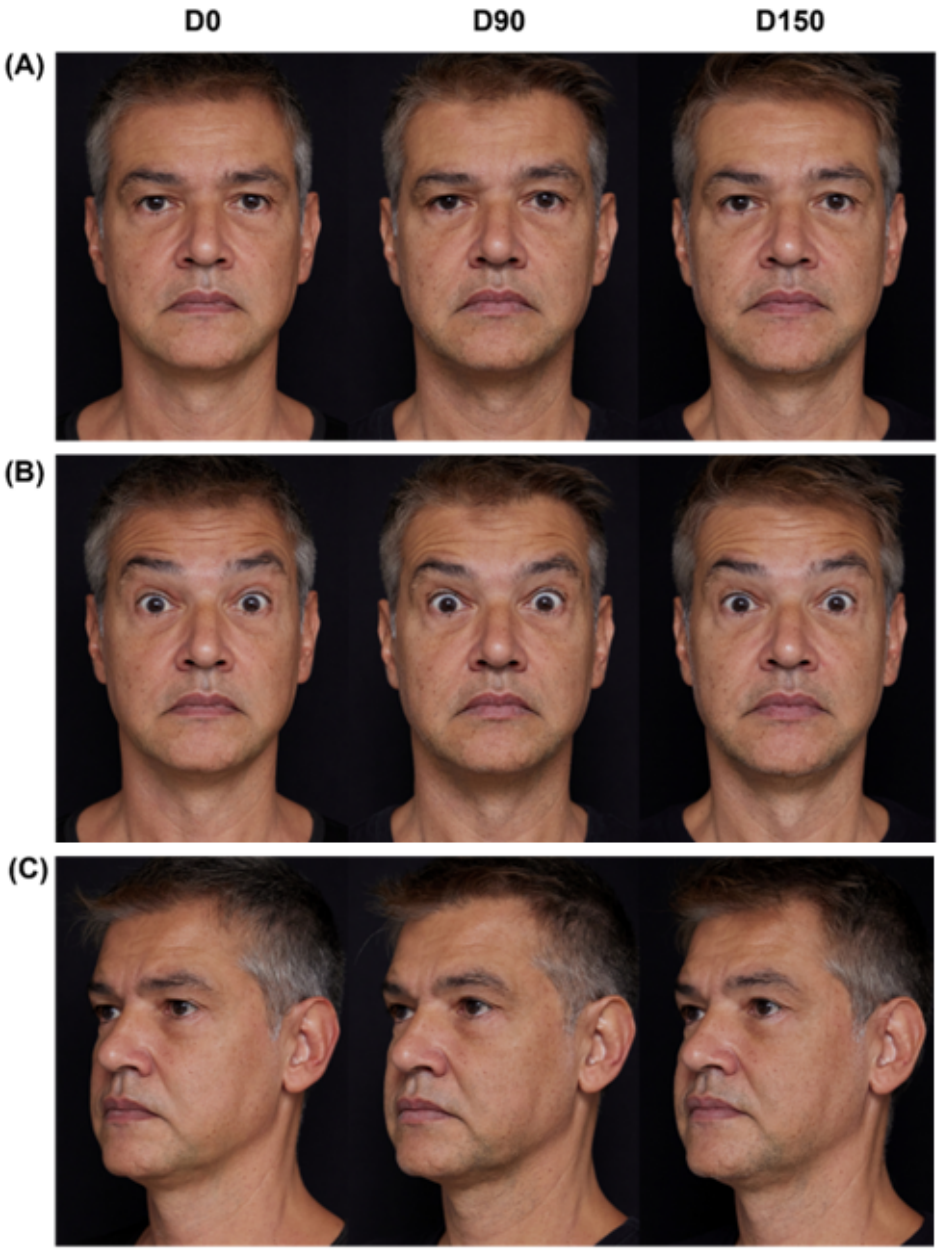
Photographic images of a 49-year-old female patient at Day 0 (before treatment) and after treatment at the Day 90 follow-up visit are shown in **Figure 2A**. Clinical assessment of these images revealed a clear improvement in forehead lines and glabellar frown at Day 90 (post-treatment) versus Day 0 (before treatment). In addition, treatment with HCC led to a clear improvement in static and dynamic (after corrugator activation) wrinkles. Photographic images of a 44-year-old male patient at Day 0 (before treatment) and after treatment at the Day 90 follow-up visit are shown in **Figure 2B**. The images show a clear improvement in eyebrow ptosis, skin firmness and skin brightness post-treatment. In addition, increased skin resistance to pinch test has been demonstrated, as clinically evaluated by the investigator (**Video 3**).



The patients provided informed consent for use of these images for scientific research.

Figure 2: Photographic images of a 49-year-old female patient (A) and a 44-year-old male patient (B) on Day 0 (before treatment) and after treatment at the Day 90 follow-up visit (yellow arrows indicates increased eyebrow elevation).

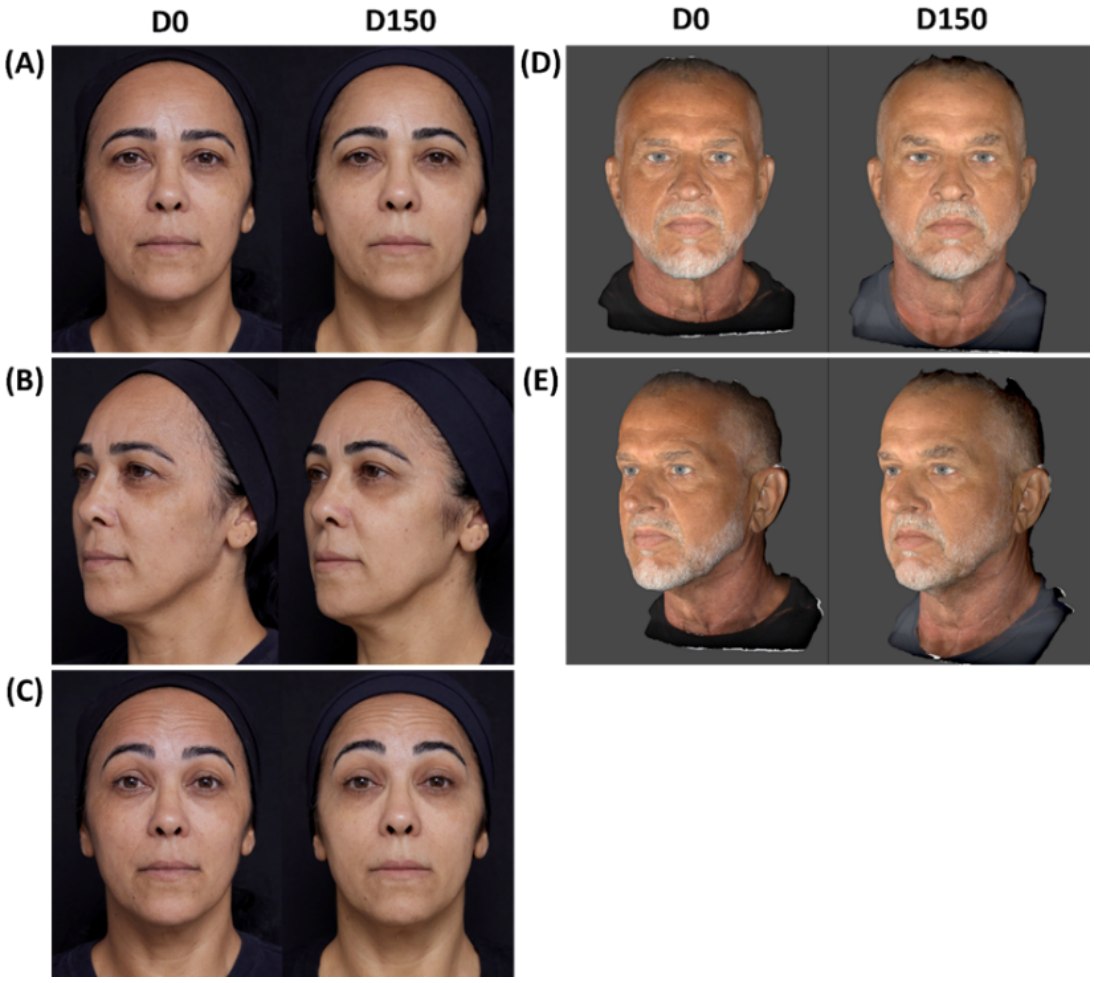
Figure 3A and **Figure 3B** show photographic images of a 54-year-old male patient with his face at rest and maximum eyebrow elevation at Day 0 (before treatment) and at the Day 90 follow-up visit. Clinical assessment of these images showed that treatment led to a clear improvement in forehead lines and static and dynamic wrinkles, after frontalis muscle activation. The side view image, taken at a 45-degree angle, also shows an impressive decrease in eyelid ptosis on Day 90, and an improvement of the jowls and jawline definition on Day 150 (**Figure 3C**).



The patient provided informed consent for use of these images for scientific research.

Figure 3: Photographic images of a 54-year-old male patient on Day 0 (before treatment) and after treatment at the Day 90 follow-up visit. Front view of his face at rest (A) and at maximum eyebrow elevation (B). Side view of the same patient with his face at rest (C).

Although patients were treated in the upper third region of their faces with HCC, for some patients, the injections also benefited the lower two-thirds of the face. A front and side view of a 48-year-old female patient before treatment on Day 0 and at the Day 150 follow-up visit is shown in **Figures 4A-C**. These images show an overall improvement in the skin quality of the periorbital region. The side view image (**Figure 4B**) indicates that there was an improvement of the eyelid ptosis and in the skin quality of the lower eyelid. The patient appears to be able to elevate her eyebrows higher at Day 150 versus Day 0 (**Figure 4C**), indicating that the contraction of the frontalis muscle has elevated the forehead region in a more vertical fashion post-treatment. A front and side view of a 63-year-old male patient with his face at rest before treatment on Day 0 on Day 150 is shown in **Figure 4D** and **Figure 4E**. The images show that the patient's eyebrows are positioned higher on Day 150 versus Day 0, and the lines on this patient's forehead and glabella are less visible. Treatment in the temple area has also yielded improvements to the quality of the skin in this patient's lower eyelids and the nasolabial fold. Overall, images showing patients at maximum eyebrow elevation (**Figures 2**, **3**, and **4**) demonstrate that treatment led to a change over time in the way that patients were able to contract their frontalis muscles. In the maximum frontalis muscle contraction position, there was a virtualization of the forehead lines and a raise in the eyebrow elevation.



The patient provided informed consent for use of these images for scientific research.

Figure 4: Photographic images (front view [A] and side view [B] while face is at rest, and front view while face is at maximum eyebrow elevation [C]) for a 48-year-old female patient on Day 0 (before treatment) and after treatment at the Day 150 follow-up visit. Photographic images taken by video (front view [D] and side view [E] while face is at rest) for a 63-year-old male patient on Day 0 and Day 150.

Patient satisfaction (GAIS score)

All the 10 patients completed patient satisfaction questionnaires (GAIS). At the Day 90 follow-up visit, seven of ten patients (70%) reported that their treated areas had "improved", and three of ten patients (30%) stated that their treated areas had "much improved" (**Table 1**). At the Day 150 follow-up visit, nine patients (90%) reported that their treated areas had "much improved", and one patient (10%) stated that their treated areas had "improved."

On Day 90, five of ten (50%) patients reported that their skin firmness had "improved" after treatment, and the four of ten (40%) patients stated that this parameter had "much improved". Only one patient (10%) reported no change in the firmness of their skin on Day 90. On Day 150, four patients (40%) reported that their skin firmness had "much improved", five patients (50%) stated that their skin firmness had "improved", and one patient (10%) reported "no change" in the firmness of their skin. On Day 90, most patients (6 of 10; 60%) also reported that the brightness of their skin had "much improved". Two patients (20%) stated that the brightness of their skin had "improved", and two patients (20%) reported "no change" in this parameter. On Day 150, six patients (60%) reported that their skin brightness had "improved," and four patients (40%) stated that this parameter had "much improved." In terms of appearance, most patients on Day 90 (seven of ten; 70%) stated that this had "much improved", and three patients (30%) reported that their appearance had "improved." On Day 150, six patients (60%) reported that their appearance had "much improved", and four patients (40%) stated that their appearance had "improved."

VAS score for pain immediately after injections

VAS questionnaires were completed immediately after treatment and the day after. On Day 0, all patients but one patient with moderate pain (VAS score for pain of 4) had mild pain (VAS score for pain of 1-3) immediately post-injections; most patients (7 of 10; 70.0%) had a low VAS score for pain of 1, one patient (10.0%) had a VAS score for pain of 2, one patient (10.0%) had a VAS score for pain of 3, and one patient (10.0%) had a VAS score for pain of 4 (**Table 1**). Similarly, all patients had mild VAS scores for pain on Day 30, with most patients (7 of 10; 70.0%) reporting a VAS score for pain of 1 immediately post-injection. All ten patients confirmed they would recommend this treatment to their family or friends (**Table 1**).

Safety outcomes

None of the patients in the case series had unexpected or serious adverse events. All patients experienced mild to moderate edema on their treated areas on the day after the procedure, as expected. All swelling were reported by the patients to have disappeared within 1–4 days. One participant had a small bruise in the surrounding eye area.

Video 1: Injection procedure for anesthetic treatment and HCC injection into forehead and temple areas.

https://www.gavinpublishers.com/assets/videos/Coimbra-et-al-Video-1.mp4

After injecting a lidocaine solution in the entry points and areas of treatment, as described above, the product was placed in the superficial subcutaneous plane, as close as possible to the dermis, using a 22Gx50mm cannula.

Video 2: An ultrasound scan taken for a patient pre-injection, during injection and immediately post-injection on Day 0.

https://www.gavinpublishers.com/assets/videos/Coimbra-et-al-Video-2.mp4

Injection with HCC of high and low molecular weight hyaluronan (Profhilo®) was assessed using an ultrasound scan (Versana Premier, GE Healthcare, Chicago, Illinois, US). During the injection procedure, the ultrasound scan was used to verify that the cannula was positioned in the subcutaneous layer. After the injection procedure, the ultrasound scan was used to confirm that the product is well positioned.

Video 3: Skin elasticity evaluated by investigator using pinch test before treatment (left side) and after treatment at day 150 (right side).

https://www.gavinpublishers.com/assets/videos/Coimbra-et-al-Video-3.mp4

Patient	Age* (years)	Sex	Race	GAIS at Day 90 and Day 150				VAS score for pain		Recommended treatment?‡
				Treated areas	Firmness	Brightness	Appearance	Immediately after treatment†	On the day after treatment†	
1	62	Male	White	Day 90: Improved Day 150: Much improved	Day 90: Improved Day 150: Much improved	Day 90: Improved Day 150: Improved	Day 90: Improved Day 150: Improved	1	1	Yes
2	49	Female	White	Day 90: Improved Day 150: Much improved	Day 90: Improved Day 150: Much improved	Day 90: Much improved Day 150: Much Improved	Day 90: Much improved Day 150: Much improved	1	1	Yes
3	48	Female	White	Day 90: Much improved Day 150: Much improved	Day 90: Much improved Day 150: Much improved	Day 90: Much improved Day 150: Much improved	Day 90: Much improved Day 150: Much improved	1	1	Yes
4	44	Male	Black	Day 90: Improved Day 150: Much improved	Day 90: Improved Day 150: Improved	Day 90: Improved Day 150: Improved	Day 90: Much improved Day 150: Improved	1	1	Yes
5	57	Female	White	Day 90: Improved Day 150: Improved	Day 90: No changes Day 150: No changes	Day 90: No change Day 150: Improved	Day 90: Improved Day 150: Much improved	2	3	Yes
6	63	Female	White	Day 90: Improved Day 150: Much improved	Day 90: Improved Day 150: Much improved	Day 90: No change Day 150: Much improved	Day 90: Improved Day 150: Much improved	3	2	Yes
7	71	Female	White	Day 90: Improved Day 150: Much improved	Day 90: Much improved Day 150: Improved	Day 90: Much improved Day 150: Improved	Day 90: Much improved Day 150: Much improved	1	1	Yes
8	41	Female	Black	Day 90: Much improved Day 150: Much improved	Day 90: Much improved Day 150: Improved	Day 90: Much improved Day 150: Improved	Day 90: Much improved Day 150: Improved	1	2	Yes
9	55	Male	White	Day 90: Much improved Day 150: Much improved	Day 90: Improved Day 150: Improved	Day 90: Much improved Day 150: Much improved	Day 90: Much improved Day 150: Much improved	4	1	Yes
10	41	Female	White	Day 90: Improved Day 150: Much improved	Day 90: Much improved Day 150: Much improved	Day 90: Much improved Day 150: Improved	Day 90: Much improved Day 150: Improved	1	1	Yes

*At baseline. †Values provided were the same after each treatment session. NR, not reported. ‡Recommendation by the patient.
GAIS, Global Aesthetic Improvement Scale; VAS, Visual Analogue Scale. GAIS is a five-point scale to score appearance improvement after aesthetic treatment vs before treatment. Possible ratings for GAIS were “very much improved”, “much improved”, “improved”, “unchanged”, or “worsened”. Possible VAS scores ranged from 0 (no pain) to 10 (worst pain).

Table 1: Patient characteristics, patient-evaluated GAIS at Days 90 and 150, and patient-evaluated VAS score for pain assessed immediately after treatment and the day after treatment.

Discussion

For ten patients aged 41-71 years included in the retrospective case series, photographic images taken before treatment and after treatment (on Day 90 and 150) with HCC of high and low molecular weight hyaluronans (Profhilo®) showed an improvement after treatment in some patients with regards to their forehead lines, glabellar frown, static and dynamic (after frontalis muscle activation) wrinkles, eyebrow ptosis, skin firmness, skin brightness, and skin quality of the periorbital region. Our study demonstrated that HCC had a positive impact on patients' contraction of the frontalis muscles. Virtualization of the forehead lines was observed during eyebrow elevation in the maximum frontalis muscle contraction position. Despite treatment in the upper third region of the face, the HCC injection also appeared to lead to an improvement in the lower two-thirds of the face such as skin quality of the lower eyelids (fine lines and hyperpigmentation), nasolabial folds, and in some patients, jowls and jawline definition.

For the present evaluation, patients were injected into forehead and temple regions using the cannula via a fanning technique [14] and injecting 1 mL for each side of the forehead and 1 mL for each side of the inferior temporal region. However, depending on individual anatomical differences and/or ethnicity, different injection volumes could also be evaluated. In particular, a volume range of 0.6 – 1 ml for each side of the forehead and a volume range of 0.4 – 1ml for each side of the inferior temporal region could be evaluated depending on patients' individual characteristics.

Patient satisfaction questionnaires (GAIS) completed at the Day 90 and Day 150 follow-up visits showed that most patients noticed that their treated areas are "improved" or "much improved" in terms of skin firmness, skin brightness and global appearance both on Day 90 and Day 150. As expected from a published post-marketing experience with HCCs with high- and low-molecular-weight hyaluronans (Profhilo®) [12], no unexpected/serious adverse events were reported for patients in this case series. Furthermore, all ten treated patients indicated that they would recommend this treatment to others.

The improvement in the contraction of frontalis muscles observed in our case series may be attributed to an improvement in the skin laxity of treated regions or be a direct effect of the product itself on the muscle, thanks to a myomodulation effect. Myomodulation involves strategically placing a dermal filler in the area of the facial mimetic or sphincter muscles to facilitate or hinder muscle action [17]. In our case series, treatment in the upper third region of the face with HCC also benefited the lower two-thirds of the face in some patients, with improvements seen in the skin quality of the periorbital region, lower eyelid, and nasolabial fold. In an in vitro study to assess the effect of hyaluronan-based gels on muscle cells derived from rats, HCCs of high- and low-molecular weight hyaluronans inhibited or counteracted biochemical pathways associated with cell stress and damage, preserving viability, phenotype, and overall functionality, demonstrating the potential of hyaluronan to treat muscle atrophy [15].

Moreover, HCC showed their potential for better global bioremodeling performance even using human dermal keratinocyte and fibroblast cell cultures and to be more stable to enzymatic attack versus linear hyaluronans, despite the absence of chemical cross linking in HCCs [16].

Outcomes from this retrospective case series are similar to the results of prior published studies. In a prior retrospective, observational study of 11 women who received HCCs of high- and low-molecular-weight hyaluronans (Profhilo®), facial skin hydration, elasticity, and trans epidermal water loss values significantly improved one month after treatment and three months post-treatment versus baseline ($P<0.01$) [10]. In addition, patients were "very satisfied" with the results after treatment and no local side effects were reported [10]. Although administered in the neck rather than the face, a single-centre clinical trial of two injections of HCCs of high- and low-molecular-weight hyaluronans (Profhilo®; administered one month apart) in 25 women aged 40-65 years with mild/moderate neck skin roughness/laxity, showed that all participants had a statistically significant improvement in their skin in this region at one and four months after the first injection [18]. Furthermore, skin improvements observed after the first injection in that trial were further enhanced after the second injection and at the last follow-up visit [18].

Findings with HCCs of high- and low-molecular-weight hyaluronans (Profhilo®) also compare well with similar marketed products. In a split-face, single-blinded study of this HCC versus a cohesive polydensified matrix hyaluronic acid comprising a slightly cross-linked hyaluronic acid (20 mg/ml) with glycerol (17.5 mg/ml), both products demonstrated an improvement compared with baseline for surface hydration, elasticity, and melanin levels [19]. In that study, HCC also significantly improved pore count and haemoglobin levels versus baseline [19].

Overall, findings from this retrospective case series indicate that HCCs of high- and low-molecular weight hyaluronans (Profhilo®) is a safe and effective treatment for the rejuvenation of the upper third of the face in men and women with a wide age range. This product is suitable for adult patients of all ethnic groups, genders, and ages.

The findings described herein are limited by the fact that this is a retrospective case series rather than a prospective clinical trial, there was no control arm to compare the administered treatment with no treatment or alternative therapy, and the case series was performed at a single institution and included a small sample size

of patients, and a few males versus females. Future studies with HCCs of high and low molecular weight hyaluronans (Profhilo®) could involve a prespecified study design and a controlled study with a control arm and a larger sample size. Despite the limitations of this case series, in line with other published studies, this real-world case series describes, in detail, an effectiveand safe technique for the injection of HCCs of high- and low-molecular-weight hyaluronans (Profhilo®) by a clinical expert to the upper third region of the face for skin regeneration of the forehead and temples.

Author contributions: Dr Daniel Dal'Asta Coimbra contributed to the conceptualization of the case series, data collection, interpreting the data, drafting, and revising the manuscript, and approving the final article for publication.

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Conflict of interest statement: Daniel Dal'Asta Coimbra is a speaker for IBSA Farmaceutici Italia Srl.

Data availability statement: The author confirms that the data supporting the findings of this study are available within the article and its supplementary appendix. Further data can be provided upon reasonable request.

Ethics statement: This retrospective case series was conducted in accordance with the Declaration of Helsinki. For this retrospective case series, informed consent was obtained from all subjects involved, before they participated in the evaluations. Written informed consent has been obtained from the patients to publish this paper. Patients also provided informed consent to use photographic/video images for scientific research.

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