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Same-Day Hyaluronic Acid Filler Followed by Laser for Facial Rejuvenation: A Prospective Three-Arm Comparative Study

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ABSTRACT

Introduction: Facial aging results from multiple levels of tissue changes. Fractional laser resurfacing and hyaluronic acid (HA) filler represent two possible complementary treatment methods, although research on a same-day treatment approach with HA followed by laser application remains scarce.

Objective: To compare the efficacy and safety of same-day sequential HA filler followed by Alma Hybrid laser with Alma Hybrid laser alone and HA filler alone.

Methods: A prospective, single-center, open-label, three-arm comparative study included 45 women aged 38 to 54 years (15 per group, mean =X). Participants were assigned sequentially according to enrollment order, using a prespecified repeating A:B:C sequence, to one of three single-session interventions: HA filler followed immediately by Alma Hybrid laser; Alma Hybrid laser alone; or HA filler alone. Three independent physicians, blinded to treatment assignment, scored standardized photographs obtained at baseline and at 1, 3, and 6 months using GAIS, FWS, WSRS, TRRS, and FVLS. Participant-reported outcomes, procedural pain, and adverse events were also assessed.

Results: At 3 months, 43 of 45 participants met the GAIS responder criterion (95.6%; 95% CI, 85.2%-98.8%), exceeding the prespecified 70% success threshold. Response rates were 100.0%, 93.3%, and 93.3% in the combination, laser-only, and HA-only groups, respectively ($P = 0.593$). All clinical scales improved over time ($P < 0.001$), with peak improvement at 3 months and sustained improvement relative to baseline at 6 months; no significant group-by-time interactions were observed. Thus, the combination treatment was not statistically superior to either monotherapy. Participant-perceived improvement was higher in both laser-containing groups than in the HA-only group ($P < 0.001$). Mean procedural pain was highest in the combination group. Twenty participants (44.4%) experienced at least one mild adverse event, and no serious adverse events occurred.

Conclusion: All three interventions were associated with improvement over 6 months. Same-day HA filler followed by Alma Hybrid laser was feasible and was not associated with serious adverse events; however, it was not statistically superior to laser-only or HA-only treatment.

Keywords: facial rejuvenation; hyaluronic acid filler; fractional laser; combination therapy; treatment sequence

INTRODUCTION

Facial aging process involves several factors acting across different tissue planes, including the skeleton, ligaments, muscles, adipose tissue, and skin [1]. On a superficial level, photoaging involves dermal and epidermal changes, including wrinkles, mottled hyperpigmentation, telangiectasias, and alterations in collagen, elastic fibers, and proteoglycans [2]. At deeper levels, aging occurs through region-specific soft-tissue atrophy in the areas around the eyes (periorbital), forehead, cheeks, temporal region, lower jawline, chin, glabella, and lips [3]. Resorption of bone takes place in the orbital rims, middle third of the face, maxillae, pyriform area, and anterior mandible, which decreases the structural support of the tissues covering the bone [4]. These processes result in tear trough deformities, periorbital wrinkles, barcode wrinkles, temporal volume loss, and perioral volume loss.

Since aging affects different tissue planes, a single modality may not fully address both epidermal and dermal issues [3]. Traditional CO2 laser ablation has achieved significant improvements in facial skin condition; however, it requires prolonged recovery and is associated with complications such as scarring and pigmentary changes [2]. Fractional ablative CO2 procedures, it uses a wavelength of 10,600 nm that targets water molecules, leading to ablation and thermal injury to tissues. The laser-induced injury preserves the untreated skin between micro-spots, reducing recovery time and side effects and leads to re-epithelialization, collagen contraction, and remodeling of the extracellular matrix [2,6]. Non-ablative fractional lasers in the 1540-1570 nm wavelength range, are commonly used for photodamage, fine rhytids, acne scarring, and textural irregularities. These mid-infrared wavelengths are absorbed primarily by water and produce arrays of microscopic thermal zones within the dermis while largely preserving the epidermal surface. The resulting controlled dermal injury initiates wound-healing cascades inducing collagen remodeling via dermal coagulation with minimal epidermal damage [5,6]. Compared with the ablative technique, the non-ablative procedure requires less downtime; however, improvement may occur gradually. In a case series, fractional non-ablative treatment of periorbital wrinkles resulted in a moderate improvement in skin texture. Ablative CO_2 laser uses a wavelength of 10,600 nm that targets water molecules, leading to ablation and thermal injury to tissues. The laser-induced injury leads to re-epithelialization, collagen contraction, and remodelling of the extracellular matrix [2,6].

The Alma Hybrid technology incorporates 10,600 nm ablative fractional wavelength along with 1,570 nm non-ablative fractional wavelength. The aim of using this combination is to create a balanced visible improvement in skin condition while significantly reducing the downtime.

Another method of treatment for aging faces is the use of HA filler. HA fillers are used to restore soft tissue volume in the face [7]. As a member of the non-sulfated glycosaminoglycans, HA is naturally present in the extracellular matrix and, due to its high affinity for water, helps hydrate and restore volume in aging patients.3 Cross-linking of HA helps prevent enzyme degradation, stress, free radical damage, and heat damage. HA filler concentration and properties determine injection depth, which defines the indication for its use [3].

In this study, region-specific HA fillers, Revanesse, were used to treat tear-trough, temporal, and perioral wrinkles. The rationale for combining laser resurfacing with HA filler is the complementary action of the two procedures. Laser treatment improves epidermal and dermal irregularities, while HA fillers provide instant correction and help to restore tissue structure, hydration, and volume. Although it remains controversial whether mechanical stress induced by filling influences fibroblasts' function, some studies indicate that HA fillers undergo morphological changes following

injection and progress through several stages until complete incorporation into tissue.8 A previous study found that a combination of cross-linked HA filler with an energy-based device improves facial appearance; preclinical evidence shows a connection between energy-based stimulation and HA metabolism [9,10].

Despite the potential benefits of using a laser and HA filler, there is little evidence for this combination as a same-day procedure. Evidence suggests that if laser and filler procedures are performed on the same day, the laser should be performed before filler injections, since interactions between energy-based treatments depend on various parameters, including laser wavelength, pulse duration, tissue depth, injection plane, and post-injection manipulation.3 However, Kim et al. found that immediate 1,064-nm picosecond fractional laser treatment after HA injection did not affect filler morphology or result in any adverse events [11].

This study aimed to explore a novel treatment sequence of filler first, followed by fractional CO2 ablative and 1,570 nm non-ablative fractional laser wavelengths.

Study Design

This prospective, single-center, open-label, three-arm comparative study evaluated the efficacy and safety of same-day HA filler followed by Alma Hybrid laser compared with Alma Hybrid laser alone and HA filler alone. Treatment targeted the periorbital, temporal, and perioral regions, including dark circles, wrinkles, barcode lines, and facial volume loss. Each participant underwent one treatment session and was followed for 6 months.

Ethical Aspects

Prior to recruitment, this clinical study obtained approval from the ethics committee of Shamir Medical Center (approval number 0048-25-ASF).

Participants

Inclusion criteria included adults aged between 38 and 55 years, Fitzpatrick skin types I-VI, seeking improvement in their facial appearance without prior aesthetic facial procedure in the last eight months. Eligible participants were required to have a score of at least 3 on the Fitzpatrick Wrinkle Scale (FWS) as evaluated by the investigator. Prior to any activity subjects provided a signed informed consent and release forms for study photography/videography.

Main exclusion criteria included recent facial aesthetic treatment within the past eight months, active local infection, sun sensitivity/photosensitivity skin disorders, unstable epithelium, pregnancy or intention for pregnancy, postpartum period or post-breastfeeding less than six weeks ago, unable to avoid excessive exposure to sunlight or tanning beds, tendency to post-inflammatory hyperpigmentation, keloid formation, wound healing problems, coagulation disorders or use of anticoagulants or antiplatelets without a wash-out approved by the Investigator, current active cancer or skin cancer history.

STUDY DEVICES AND MATERIALS

Laser treatment was delivered using the Alma Hybrid system (Alma Lasers, Israel) with the ProScan applicator in HyGrid mode, which combines 10,600-nm ablative fractional CO2 and 1,570-nm non-ablative fractional wavelengths. A 1:1 ablative-to-non-ablative ratio was applied. The study-specific settings were: CO2 power of 20-25 W and pulse duration of 0.8-1.2 ms; 1,570-nm power of 10-12 W, and pulse duration of 3-4 ms. For treatment with the dermal

filler, Revanesse products (Prollenium Medical Technologies Inc., Canada) were used: Revanesse Revise for the tear troughs, Revanesse Contour for the temples, and Revanesse Kiss for the barcode wrinkles. Product selection and volume were based on the treated region within the predefined limits shown in Table 1.

Treatment Assignment and Procedure

After eligibility was confirmed, participants were assigned sequentially according to enrollment order using a prespecified repeating A:B:C sequence: the first participant was allocated to Group A, the second to Group B, the third to Group C, and the sequence was then repeated. This was a deterministic sequential allocation procedure, not randomization. Each participant underwent one treatment session. Product identity, injection volume, laser settings, anesthesia, post-procedure care, and medications used to manage adverse events were recorded in the case report form.

Table 1: Study groups and interventions

Group	Study arm	Treatment protocol
A	Same-day sequential HA filler + Alma Hybrid laser	Revanesse Revise for tear trough: 0.5-1 mL per side; Revanesse Contour for temple: 1-2 mL per side; Revanesse Kiss for barcode wrinkles: 1-2 mL. HA filler injection was followed by Alma Hybrid treatment using the 1:1 ratio and study-specific parameters reported in the Study Devices and Materials section.
B	Alma Hybrid laser only	Alma Hybrid treatment using the 1:1 ratio and study-specific parameters reported in the Study Devices and Materials section.
C	HA filler only	Revanesse Revise for tear trough: 0.5-1 mL per side; Revanesse Contour for temple: 1-2 mL per side; Revanesse Kiss for barcode wrinkles: 1-2 mL.

Study Procedures and Follow-Up

Screening included demographic details, Fitzpatrick skin type, past medical history, concomitant medications, and an assessment of eligibility. Participant eligibility was determined no more than two weeks prior to the first treatment session. Two-dimensional photographs were taken at baseline and at each follow-up appointment under controlled lighting conditions, from identical angles, and with the participant in the same position.

Three independent, non-treating physicians who were blinded to treatment assignment scored standardized photographs obtained at baseline and at the 1-, 3-, and 6-month follow-up visits using the protocol-specified scales. Analyses used the mean of the three blinded assessor ratings.

Primary and Secondary Outcomes

The primary efficacy outcome was the percentage of participants achieving an overall improvement of "improved" on the GAIS scale (GAIS ≥3) at 3 months follow-up, relative to baseline. The predefined success criterion for the study was a responder rate of at least 70%.

Secondary efficacy measures included GAIS improvement at 1 month and at 6 months; severity of wrinkles, quantified by the FWS class, FWS wrinkling score, and WSRS; tear trough severity, quantified by the TRRS, which includes measurements of severity, hyperpigmentation, fat pad prolapse, and lower eyelid rhytidosis; and facial volume loss measured by FVLS. Lower scores for FWS, WSRS, TRRS, and FVLS indicate an improvement.

Participants' self-assessments involved perceived improvement, treatment satisfaction, and intention to recommend treatment to others. Satisfaction was reported at 1, 3, and 6 months. Perceptions of improvement and recommendation intentions were reported at 3 months. Immediate post-procedural pain was assessed using the 11-point NPRS (from 0, absence of pain, to 10, worst possible pain).

Safety Measures

Potential AEs and SAEs were monitored from informed consent through the completion of follow-up visits. For each event, the dates of onset and resolution, actions taken, event outcomes, side-effect intensity, and causality to the study intervention were reported. Intensity could be mild, moderate, or severe, while causality was categorized as not related, unlikely, possible, probable, or definite. Expected laser side effects included crusting, erythema, edema, pain, heat sensation, pigmentation change, pruritus, ocular damage, and scarring. Expected injection side effects included pain, swelling, bruising, warmth, stiffness, nodules, allergy, infection, migration, inflammation, tissue rejection, and vascular occlusion.

Statistical Analyses

The GAIS baseline was defined as the last valid pre-treatment assessment. All 45 allocated participants provided complete data and were included in the analyses.

Means and standard deviations were used to summarize continuous variables. Categorical variables were summarized with frequencies and percentages. One-way ANOVA was used to test differences in baseline age among study groups, while Pearson chi-square tests were used to compare categorical baseline characteristics. Results for the overall responder rate were presented as the 95% Wilson confidence interval and compared against the prespecified 70% success criterion using a one-sided exact test. Responder rates across groups were compared using Pearson chi-square tests.

For outcomes involving repeated measures over the study period, a mixed-design repeated-measures ANOVA was used, with treatment group as the between-subjects factor, time as the within-subjects factor, and participant as the repeated factor. Holm adjustment was used for post hoc comparisons. GAIS and participant-reported scores were compared across groups using the Kruskal-Wallis test, with Holm-adjusted pairwise comparisons where appropriate. Within-group changes in satisfaction were assessed using Friedman tests. Filler volumes were compared only between the combination and HA-only groups using independent-samples t tests, because the laser-only group did not receive filler. Adverse-event rates were compared using Pearson chi-square tests. Except for the one-sided primary analysis, all tests were two-sided, and $P < 0.05$ was considered statistically significant.

RESULTS

Study Participants

A total of 45 participants were sequentially allocated, with 15 in each treatment group. All participants had complete data at baseline and at all three follow-up visits. All participants were women. The mean age was 45.0 ± 4.2 years (range, 38-54 years), and Fitzpatrick skin types II and III comprised 39 of 45 participants (86.7%). There were no statistically significant differences among groups in baseline age, Fitzpatrick skin type, ethnicity, or baseline efficacy parameters (all $P > 0.05$; Table 2).

Table 2: Demographic and baseline characteristics

Characteristic	Combination (n=15)	Laser only (n=15)	HA only (n=15)	Overall (n=45)	P value
Age, years, mean ± SD	45.1 ± 4.5	44.5 ± 4.3	45.4 ± 4.3	45.0 ± 4.2	0.855
Female sex, n (%)	15 (100.0%)	15 (100.0%)	15 (100.0%)	45 (100.0%)	-
Fitzpatrick skin type I, n (%)	2 (13.3%)	0 (0.0%)	0 (0.0%)	2 (4.4%)	0.338
Fitzpatrick skin type II, n (%)	5 (33.3%)	7 (46.7%)	7 (46.7%)	19 (42.2%)	
Fitzpatrick skin type III, n (%)	8 (53.3%)	6 (40.0%)	6 (40.0%)	20 (44.4%)	
Fitzpatrick skin type IV, n (%)	0 (0.0%)	2 (13.3%)	2 (13.3%)	4 (8.9%)	
Caucasian/European, n (%)	5 (33.3%)	5 (33.3%)	8 (53.3%)	18 (40.0%)	0.103
Mediterranean, n (%)	2 (13.3%)	7 (46.7%)	2 (13.3%)	11 (24.4%)	
Middle Eastern, n (%)	6 (40.0%)	3 (20.0%)	5 (33.3%)	14 (31.1%)	
Mixed/Other, n (%)	2 (13.3%)	0 (0.0%)	0 (0.0%)	2 (4.4%)	

P values were calculated using one-way analysis of variance for age and Pearson chi-square tests for categorical variables. Percentages may not total 100% because of rounding. HA, hyaluronic acid; SD, standard deviation.

Primary Efficacy Endpoint

At 3 months, 43 of 45 participants met the protocol-defined GAIS responder criterion, corresponding to an overall responder rate of 95.6% (95% CI, 85.2%-98.8%). This exceeded the prespecified 70% success criterion (one-sided exact P<0.001). Responder rates were 100.0% (15/15) in the combination group, 93.3% (14/15) in the laser-only group, and 93.3% (14/15) in the HA-only group, with no significant between-group difference (P=0.593). Mean GAIS scores at 3 months were 3.73 ± 0.70, 3.60 ± 0.91, and 3.47 ± 0.83, respectively (P=0.616).

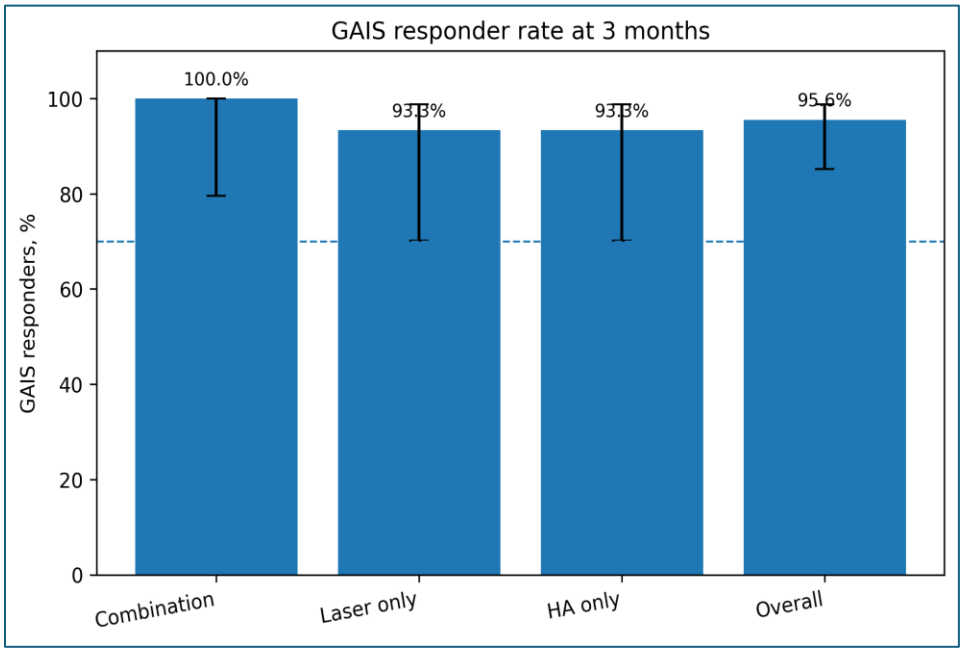

Figure 1: GAIS responder rates at the 3-month follow-up. Responders had GAIS ≥3. Error bars show Wilson 95% confidence intervals; the dashed line denotes the prespecified 70% success criterion.

Secondary Clinical Efficacy Outcomes

All prespecified clinical measures changed significantly over time (all time effects, P < 0.001). No significant group-by-time interactions were observed for FWS class, FWS wrinkling score, WSRS grade, TRRS components, or FVLS grade (interaction P values, 0.352-0.711).

At 1 month, changes from baseline were small but significant in all three groups for all efficacy measures (Holm-adjusted P ≤ 0.008), with no between-group differences in change from baseline (P = 0.572-0.977). At 3 months, each group achieved its greatest mean improvement. For each measure, the numerical reduction from baseline was greater in the combination and laser-only groups than in the HA-only group, but the between-group differences were not statistically significant (P = 0.223-0.492). Changes from baseline within each group were significant (Holm-adjusted P ≤ 0.001).

At 6 months, all three groups remained significantly improved relative to baseline (Holm-adjusted P ≤ 0.008), although improvement was smaller than at 3 months (Holm-adjusted P ≤ 0.006). Between-group differences in change from baseline remained nonsignificant (P = 0.079-0.611). Representative clinical photographs are shown in Figures 5-7.

Table 3: Wrinkle and volume outcomes by treatment group and follow-up visit

Outcome	Group	Baseline	1 month	3 months	6 months	P for time	P for group x time
FWS class	Combination	2.47 ± 0.29	2.39 ± 0.29	2.03 ± 0.45	2.26 ± 0.35	<0.001	0.518
	Laser only	2.44 ± 0.30	2.35 ± 0.33	2.02 ± 0.48	2.23 ± 0.40		
	HA only	2.37 ± 0.24	2.28 ± 0.28	2.05 ± 0.39	2.22 ± 0.31		
FWS wrinkling score	Combination	5.61 ± 0.70	5.18 ± 0.74	4.47 ± 1.06	4.99 ± 0.89	<0.001	0.633
	Laser only	5.62 ± 0.87	5.21 ± 0.91	4.51 ± 0.86	4.97 ± 1.02		
	HA only	5.49 ± 0.67	5.13 ± 0.66	4.61 ± 0.85	5.06 ± 0.85		
WSRS grade	Combination	3.35 ± 0.36	3.13 ± 0.47	2.53 ± 0.55	2.93 ± 0.44	<0.001	0.549
	Laser only	3.47 ± 0.49	3.24 ± 0.65	2.69 ± 0.67	3.09 ± 0.71		
	HA only	3.41 ± 0.50	3.18 ± 0.62	2.76 ± 0.55	3.16 ± 0.53		
FVLS grade	Combination	3.19 ± 0.53	2.95 ± 0.57	2.37 ± 0.56	2.77 ± 0.57	<0.001	0.686
	Laser only	3.21 ± 0.41	3.03 ± 0.48	2.42 ± 0.53	2.83 ± 0.49		
	HA only	3.20 ± 0.50	3.00 ± 0.52	2.55 ± 0.69	2.92 ± 0.53		

Values are mean ± SD. Lower scores indicate improvement. P values are from mixed-design repeated-measures analyses with participant as the repeated factor. FWS, Fitzpatrick Wrinkle Scale; FVLS, Facial Volume Loss Scale; HA, hyaluronic acid; WSRS, Wrinkle Severity Rating Scale.

Table 4: Tear Trough Rating Scale component scores by treatment group and follow-up visit

TRRS component	Group	Baseline	1 month	3 months	6 months	P for time	P for group x time
Depth	Combination	3.29 ± 0.52	3.01 ± 0.51	2.45 ± 0.52	2.83 ± 0.49	<0.001	0.563
	Laser only	3.10 ± 0.52	2.85 ± 0.63	2.31 ± 0.65	2.73 ± 0.65		
	HA only	3.01 ± 0.60	2.77 ± 0.56	2.38 ± 0.59	2.67 ± 0.61		
Hyperpigmentation	Combination	2.77 ± 0.56	2.55 ± 0.50	2.08 ± 0.47	2.47 ± 0.59	<0.001	0.711
	Laser only	2.81 ± 0.31	2.62 ± 0.39	2.16 ± 0.51	2.51 ± 0.41		
	HA only	2.61 ± 0.41	2.43 ± 0.50	2.09 ± 0.51	2.39 ± 0.41		
Fat-pad prolapse	Combination	2.74 ± 0.45	2.55 ± 0.49	2.13 ± 0.60	2.47 ± 0.54	<0.001	0.352
	Laser only	2.63 ± 0.44	2.48 ± 0.48	2.05 ± 0.49	2.34 ± 0.56		

	HA only	2.56 ± 0.59	2.38 ± 0.56	2.11 ± 0.62	2.37 ± 0.67		
Lower-eyelid rhytidosis	Combination	3.29 ± 0.30	3.04 ± 0.38	2.50 ± 0.45	2.83 ± 0.36	<0.001	0.474
	Laser only	3.12 ± 0.35	2.89 ± 0.36	2.34 ± 0.52	2.81 ± 0.43		
	HA only	3.16 ± 0.40	2.95 ± 0.53	2.56 ± 0.68	2.91 ± 0.51		

Values are mean ± SD. Lower scores indicate improvement. P values are from mixed-design repeated-measures analyses with participant as the repeated factor. HA, hyaluronic acid; TRRS, Tear Trough Rating Scale.

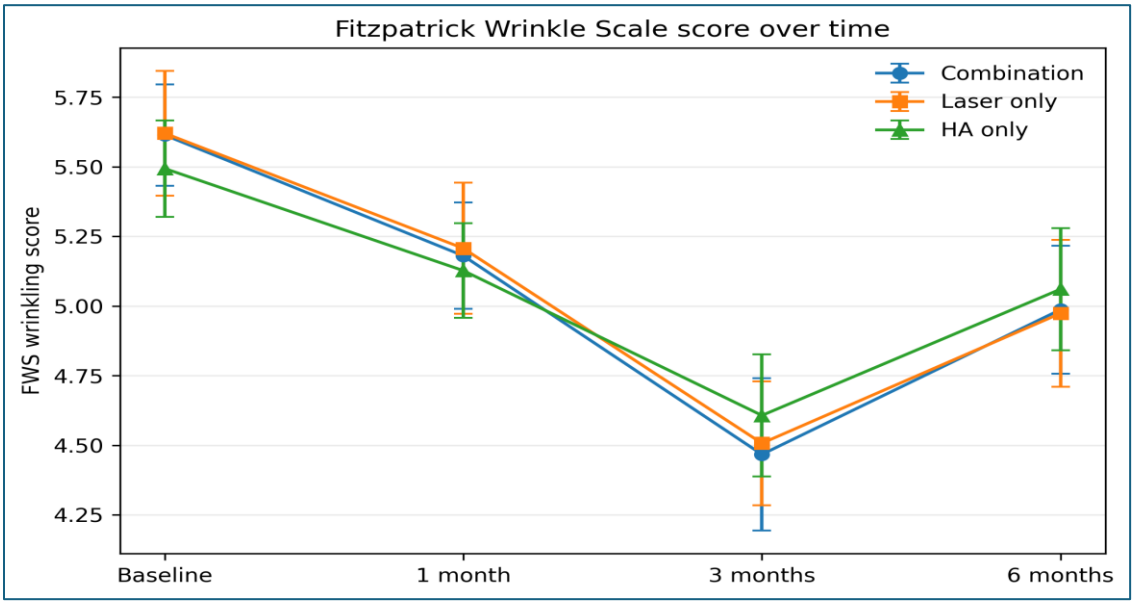

Figure 2: Mean FWS wrinkling scores over time by treatment group. Error bars represent standard errors. Lower scores indicate less severe wrinkling.

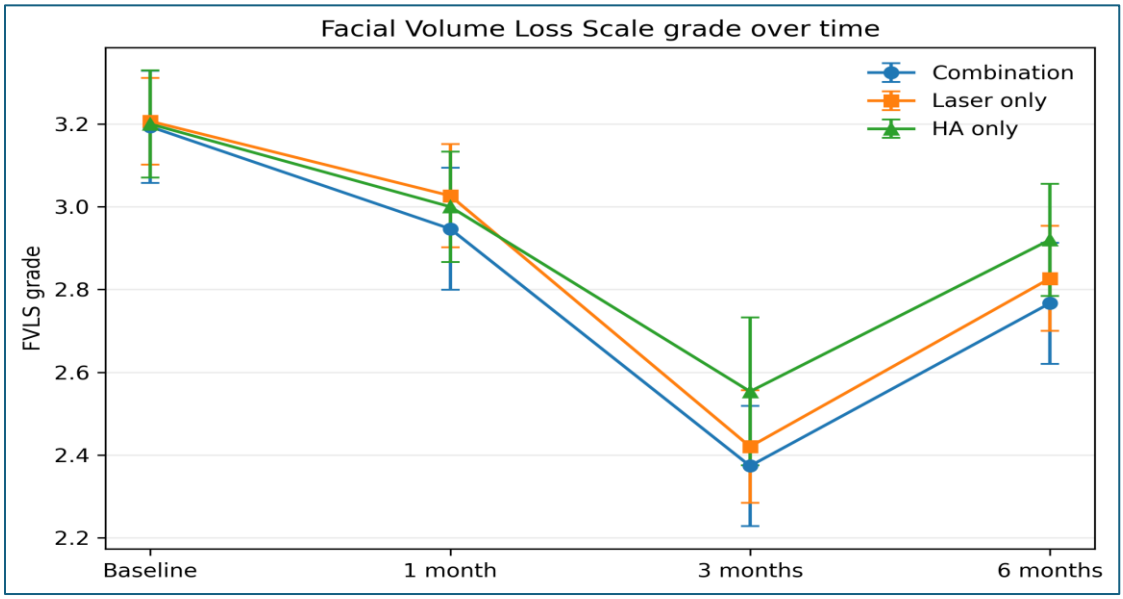

Figure 3: Mean FVLS grades over time by treatment group. Error bars represent standard errors. Lower grades indicate less facial volume loss.

GAIS Response Rate and Participant-Reported Outcomes

Overall, the GAIS responder rate increased from 62.2% at 1 month to 95.6% at 3 months and then decreased slightly to 93.3% at 6 months. At 3 months, participant-perceived improvement scores differed among groups ($P < 0.001$): 4.27 ± 0.46 in the combination group, 4.33 ± 0.72 in the laser-only group, and 3.47 ± 0.52 in the HA-only group. The combination and laser-only groups did not differ from each other (Holm-adjusted $P = 0.603$), and both laser-containing groups scored higher than the HA-only group (Holm-adjusted $P = 0.001$ and $P = 0.004$, respectively).

There was no difference in patient satisfaction and readiness to recommend the procedure among groups at 3 months ($P = 0.319$ and $P = 0.221$, respectively). Patient satisfaction showed an increasing trend from 1 month to 6 months (1.93-2.13 to 3.40-3.67 to 4.40-4.67, respectively) in all groups, as confirmed by Friedman tests ($P < 0.001$ in all cases). There were no significant between-group differences at any time point (all $P \geq 0.319$).

Table 5: GAIS and participant-reported outcomes.

Outcome	Combination (n=15)	Laser only (n=15)	HA only (n=15)	Overall (n=45)	P value
GAIS responder at 1 month, n (%)	8 (53.3%)	10 (66.7%)	10 (66.7%)	28 (62.2%)	0.685
GAIS responder at 3 months, n (%)	15 (100.0%)	14 (93.3%)	14 (93.3%)	43 (95.6%)	0.593
GAIS responder at 6 months, n (%)	14 (93.3%)	13 (86.7%)	15 (100.0%)	42 (93.3%)	0.343
GAIS score at 1 month, mean ± SD	2.67 ± 0.72	2.73 ± 0.59	2.67 ± 0.49	2.69 ± 0.60	0.907
GAIS score at 3 months, mean ± SD	3.73 ± 0.70	3.60 ± 0.91	3.47 ± 0.83	3.60 ± 0.81	0.616
GAIS score at 6 months, mean ± SD	3.20 ± 0.56	3.20 ± 0.68	3.13 ± 0.35	3.18 ± 0.53	0.865
Perceived improvement at 3 months, mean ± SD	4.27 ± 0.46	4.33 ± 0.72	3.47 ± 0.52	4.02 ± 0.69	<0.001
Subject satisfaction at 1 month, mean ± SD	2.13 ± 0.52	2.00 ± 0.53	1.93 ± 0.59	2.02 ± 0.54	0.593
Subject satisfaction at 3 months, mean ± SD	3.67 ± 0.49	3.60 ± 0.51	3.40 ± 0.51	3.56 ± 0.50	0.319
Subject satisfaction at 6 months, mean ± SD	4.67 ± 0.49	4.60 ± 0.51	4.40 ± 0.51	4.56 ± 0.50	0.319
Recommendation score at 3 months, mean ± SD	8.07 ± 0.88	7.80 ± 0.94	7.67 ± 0.90	7.84 ± 0.90	0.221

GAIS responders had scores ≥3. P values were calculated using Pearson chi-square tests for responder proportions and Kruskal-Wallis tests for ordinal or rating-scale outcomes. GAIS, Global Aesthetic Improvement Scale; HA, hyaluronic acid; SD, standard deviation.

Figure 4: Mean participant satisfaction scores during follow-up by treatment group. Error bars represent standard errors. Satisfaction increased significantly from 1 to 3 months and from 3 to 6 months in each group.

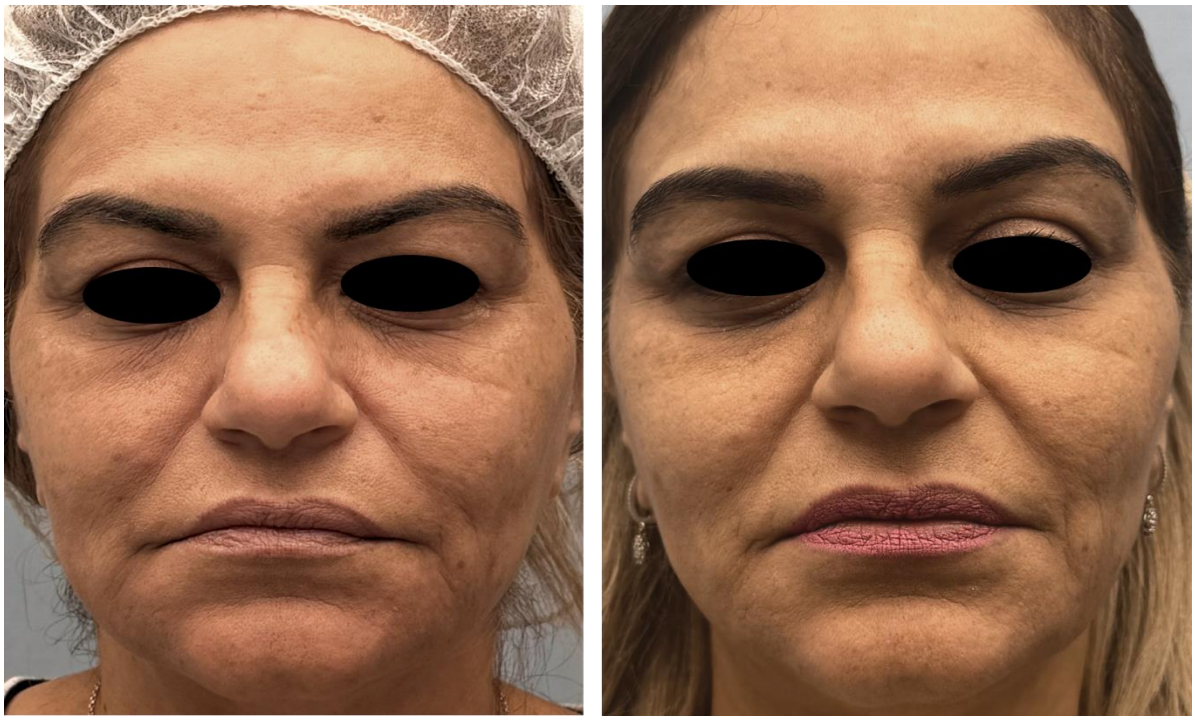

Figure 5: Representative frontal photographs at baseline (left) and 6 months after a single same-day treatment with Alma Hybrid and hyaluronic acid filler (right), demonstrating wrinkles reduction and improvement in general appearance.

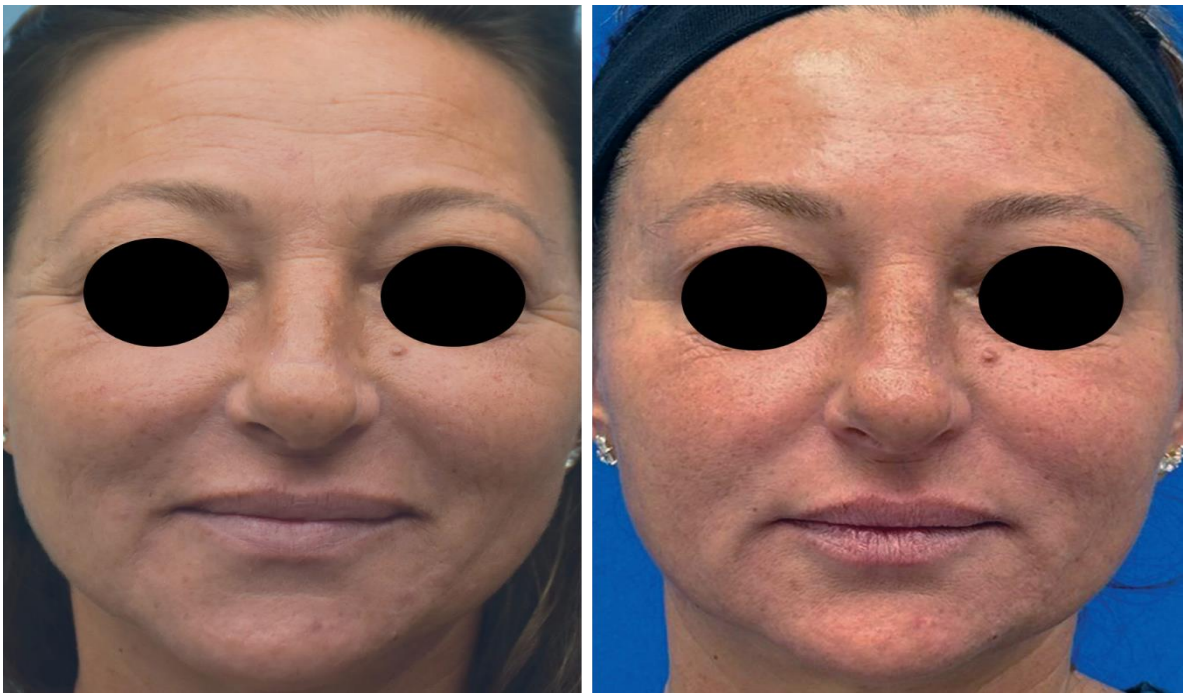

Figure 6: Frontal clinical photographs obtained before treatment (left) and 6 months after a single periorbital hyaluronic acid filler treatment (right), demonstrating a reduction in the appearance of periorbital wrinkles.

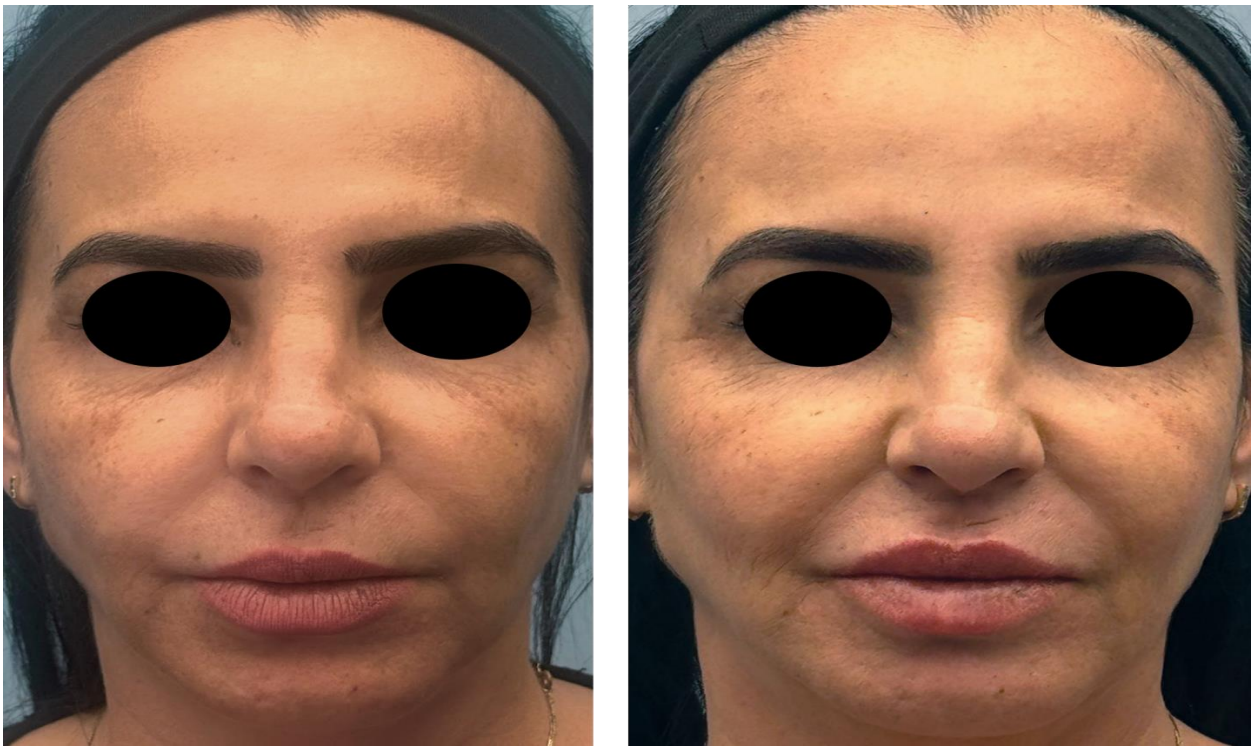

Figure 7: Frontal views at baseline (left) and 6 months after a single Alma Hybrid laser treatment (right), showing visible softening of periorbital and forehead wrinkles and improvement in overall skin texture.

Treatment Exposure, Safety, and Tolerability

Among participants who received HA filler, mean administered volumes did not differ significantly between the combination and HA-only groups for Revanesse Revise in the tear-trough region (P = 0.747), Revanesse Contour in the temple region (P = 0.534), or Revanesse Kiss in the barcode-line region (P = 0.385); the laser-only group was not included because it did not receive filler. Mean procedural pain scores were 3.43 ± 0.91, 2.65 ± 0.77, and 1.55 ± 0.85 in the combination, laser-only, and HA-only groups, respectively (P < 0.001). Pain was higher in the combination group than in the laser-only group (Holm-adjusted P = 0.038) and HA-only group (P < 0.001), and higher in the laser-only group than in the HA-only group (P = 0.003).

Twenty participants (44.4%) experienced at least one side effect. Seven participants in the combination group (46.7%), eight in the laser-only group (53.3%), and five in the HA-only group (33.3%) experienced side effects (P = 0.533). All observed side effects were mild and considered treatment-related. Erythema and edema were reported in the laser-containing groups, whereas bruising and swelling were reported in the HA-only group. No serious adverse events occurred.

Table 6: Treatment exposure, pain, and adverse events

Measure	Combination (n=15)	Laser only (n=15)	HA only (n=15)	Overall (n=45)	P value
Revanesse Revise, mL per side	0.75 ± 0.16	N/A	0.73 ± 0.13	-	0.747
Revanesse Contour, mL per side	1.58 ± 0.25	N/A	1.52 ± 0.27	-	0.534
Revanesse Kiss, total mL	1.56 ± 0.35	N/A	1.65 ± 0.22	-	0.385
Procedural pain (NPRS 0–10), mean ± SD	3.43 ± 0.91	2.65 ± 0.77	1.55 ± 0.85	2.54 ± 1.14	<0.001
Any adverse event, n (%)	7 (46.7%)	8 (53.3%)	5 (33.3%)	20 (44.4%)	0.533
Mild erythema, n (%)	3 (20.0%)	5 (33.3%)	0 (0.0%)	8 (17.8%)	-
Mild edema, n (%)	4 (26.7%)	3 (20.0%)	0 (0.0%)	7 (15.6%)	-
Mild bruising, n (%)	0 (0.0%)	0 (0.0%)	3 (20.0%)	3 (6.7%)	-
Mild swelling, n (%)	0 (0.0%)	0 (0.0%)	2 (13.3%)	2 (4.4%)	-
Serious adverse event, n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-

Values are mean ± SD unless otherwise stated. Filler-volume comparisons used independent-samples t tests between the combination and HA-only groups only; the laser-only group was not applicable. Pain was compared using the Kruskal-Wallis test, and adverse-event proportions were compared using the Pearson chi-square test. HA, hyaluronic acid; NPRS, Numerical Pain Rating Scale, N/A, not applicable.

DISCUSSION

The prespecified overall GAIS responder benchmark was met, with 43 of 45 participants (95.6%) classified as responders at 3 months. However, the principal comparative finding was the absence of statistically significant differences among the three treatment groups. All groups improved over time, and the combination treatment was not statistically superior to laser-only or HA-only treatment for GAIS, wrinkle severity, tear-trough measures, or facial volume loss. The 100.0% response rate in the combination group versus 93.3% in each monotherapy group represented a difference of only 1 participant per group and should not be interpreted as evidence of superiority, particularly given the small sample size of 15 participants per arm.

The temporal pattern of responses provided some clinically meaningful insights. The initial improvement was moderate at 1 month, peaked at 3 months, then decreased at 6 months, but remained better than baseline. It appears reasonable to link these observations to collagen remodeling resulting from the delivered fractional thermal damage, superimposed on the effects of HA injection [6]. Hybrid fractional technologies combine epidermal ablation with non-ablative dermal coagulation, thereby coupling surface regeneration with collagen remodeling [6]. HA replenishes lost volume and improves the hydration and mechanical properties of the dermis, thereby facilitating fibroblastic activity [3,12]. Thus, complementation at a biological level seems plausible. On the other hand, the lack of group by time interaction in the results precluded confirmation of synergy in this instance.

Both laser-containing groups showed descriptively greater reductions on several clinical scales than the HA-only group, but the between-group comparisons and group-by-time interactions were not statistically significant. Participant-perceived improvement at 3 months was greater in both laser-containing groups than in the HA-only group, whereas the combination and laser-only groups were similar. Because the minimal clinically important difference for this measure is unknown and the study was small, this subjective finding should be interpreted cautiously. It suggests a perceived benefit associated with inclusion of laser treatment but does not demonstrate an added benefit from combining laser with HA filler.

The sequence of treatment plays an integral role in the proper interpretation of the results. General consensus among dermatologists recommends using a laser or light prior to HA filler injection, especially if the laser energy can reach the filler plane [3]. The reasons for this include possible filler displacement or interaction with the energy, resulting in adverse outcomes [11]. On the other hand, filler injection can be beneficial for more accurate placement, whereas using energy prior to filler injection reduces risks to the filler and helps avoid post-treatment edema [3]. For example, a recent review recommended performing laser treatment before or delaying the injection of an HA-calcium hydroxyapatite injectable [13]. However, these products are not identical to the filler investigated in this research.

Limited prior evidence has suggested that immediate laser treatment after HA injection may be feasible under specific conditions. In the cited study, however, a 1,064-nm picosecond-domain fractional laser was used, not the 10,600-nm/1,570-nm Alma Hybrid protocol examined here [11]. Therefore, those findings cannot be directly generalized to the present sequence. The absence of un-anticipated adverse events in this study is reassuring, but the lack of laser-first and staged comparator groups precludes conclusions about the relative safety or efficacy of alternative sequencing approaches.

The combination group had the highest mean procedural pain score (3.43 ± 0.91 on the 0-10 NPRS), although the absolute level was modest. This difference is relevant to participant counseling and anesthesia planning. were reported in 46.7% of the combination group, 53.3% of the laser-only group, and 33.3% of the HA-only group; all were mild, and no serious adverse events were observed.

The above shows that assumptions of synergism in combination therapies should be critically evaluated before implementation. While combining multiple modes targeting different tissues in aging is reasonable based on biological considerations, reviews report benefits in volume, texture, and skin tone from combining modalities [12]. Also, according to a meta-analysis, combination of laser modalities yields greater efficacy and satisfaction than monotherapy [14]. Yet this investigation revealed no statistically significant superiority. Synergy between specific

procedures should be evaluated separately. Therefore, combination therapy may prove useful from an anatomical perspective but not always from an efficacy standpoint.

This study has several limitations. It was a small, single-center, open-label study with 15 participants per arm, deterministic sequential allocation by enrollment order, an all-female population, and a predominance of Fitzpatrick skin types II and III, which limits internal validity and generalizability. The absence of statistically significant between-group differences should not be interpreted as evidence of equivalence. The sample size was also too small to exclude uncommon or rare adverse events. In addition, the study did not include laser-first or staged-treatment comparator groups, so no conclusions can be drawn about the relative safety or efficacy of alternative sequencing strategies. Follow-up was limited to 6 months after a single treatment session, and no ultrasound, three-dimensional imaging, or histologic assessment was used to evaluate filler integrity.

These findings support further investigation rather than a definitive recommendation for a sequence. Future trials should compare filler-first, laser-first, and staged approaches; include larger and more diverse populations; extend follow-up; and incorporate ultrasound, three-dimensional imaging, or histologic assessment of filler integrity. Until comparative evidence is available, treatment sequencing should follow applicable product labeling, device instructions, and individualized clinical judgment.

CONCLUSION

All three interventions produced statistically significant improvements from baseline that were maintained through 6 months. The same-day filler-first combination achieved a high 3-month GAIS responder rate, but it was not statistically superior to laser-only or HA-only treatment. The findings support the feasibility of this sequence and identified only mild treatment-emergent adverse events.

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