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Prospective Study

Efficacy and Safety of a Multimodal Laser, Injectable, and Topical Protocol for the Treatment of Skin Hyperpigmentation: A Prospective Pilot Study

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ABSTRACT

Skin hyperpigmentation disorders are common, chronic, and often refractory to monotherapy. Multimodal strategies addressing pigmentation, dermal quality, and epidermal barrier simultaneously may improve outcomes. To evaluate the efficacy and safety of a combined protocol using accelerated non-ablative fractional diode laser therapy (LaserMe®), injectable non-cross-linked calcium hydroxyapatite-hyaluronic acid (CaHA-HA), and adjunctive topical retinoid and ascorbic acid in patients with facial hyperpigmentation. Five participants with Fitzpatrick skin types I-IV (including melasma, post-inflammatory hyperpigmentation, age-related pigmentation, and photodamage-associated dyschromia) were enrolled in a prospective, open-label pilot study. The protocol included three laser sessions over four weeks, injectable CaHA-HA at weeks 0 and 4, daily stabilised ascorbic acid, alternate-night retinoid application, and broad-spectrum SPF 50 photoprotection. The primary outcome was the change in pigmentation severity assessed by the modified Melasma Area and Severity Index (mMASI). Secondary outcomes included transepidermal water loss (TEWL), standardised photographic assessment, and safety evaluation over 12 weeks. All participants demonstrated clinically meaningful improvement in pigmentation by week 12. Mean mMASI scores decreased from 14.0 at baseline to 7.0 at week 12, representing a 50.4% mean reduction. Four of five participants showed improved TEWL values, with mean TEWL decreasing from 19.0 to 14.4 g/m²/h. No serious adverse events occurred; mild transient erythema, swelling, and bruising resolved spontaneously. This pilot study suggests that a combined laser-injectable-topical protocol is safe, well-tolerated, and associated with consistent improvements in pigmentation severity and epidermal barrier function. Larger randomised controlled trials are warranted to confirm these findings.

INTRODUCTION

Skin hyperpigmentation disorders, including melasma, solar lentigines, and post-inflammatory hyperpigmentation, constitute a substantial aesthetic concern and are associated with significant psychosocial impact. These conditions are multifactorial in pathogenesis, with contributions from ultraviolet radiation, hormonal influences, inflammatory pathways, and intrinsic aging processes. Clinically, they are characterised by chronicity, high rates of persistence, and frequent recurrence despite available therapeutic options (1-3).

Beyond melanocyte hyperactivity, hyperpigmentation disorders are increasingly understood as disorders of the epidermal-dermal unit. Emerging evidence highlights the role of altered keratinocyte signalling, basement membrane disruption, dermal inflammation, vascular involvement, and impaired epidermal barrier function in their pathophysiology (4-8). Increased transepidermal water loss (TEWL) and subclinical inflammation have been documented in both melasma and post-inflammatory hyperpigmentation, suggesting that epidermal barrier dysfunction may contribute to pigmentary relapse and reduced responsiveness to treatment (4, 5, 7, 8). These observations provide a compelling rationale for therapeutic strategies that simultaneously target pigmentation, dermal support, and epidermal barrier restoration, rather than focusing on melanin suppression alone.

Non-ablative fractional laser technologies provide a targeted therapeutic approach to pigmentary disorders by creating microscopic zones of controlled thermal injury that promote epidermal turnover and stimulate dermal remodelling while preserving adjacent tissue. This fractional injury pattern enables faster recovery and a lower risk of post-inflammatory hyperpigmentation compared with ablative laser modalities, particularly in

patients with darker skin phototypes (9-12). To further augment and sustain these effects, adjunctive interventions targeting the dermal microenvironment may offer complementary benefit.

Injectable biostimulatory and hydrating agents, including hyaluronic acid and calcium hydroxyapatite-based formulations, have demonstrated clinical benefits extending beyond volumisation. These include stimulation of fibroblast activity, neocollagenesis, and improvements in dermal quality and hydration (13-17). In particular, non-cross-linked calcium hydroxyapatite-hyaluronic acid formulations may enhance skin quality without inducing excessive volumetric change, rendering them well-suited for diffuse pigmentary and textural indications.

Topical retinoids and ascorbic acid remain cornerstone adjunctive therapies in the management of hyperpigmentation. Their mechanisms include modulation of keratinocyte differentiation, inhibition of melanogenesis, and antioxidant protection against ultraviolet-induced oxidative stress (18-22). When used in conjunction with procedural interventions, these agents may enhance overall treatment efficacy while supporting epidermal recovery and restoration of barrier function.

Despite increasing interest in multimodal strategies for hyperpigmentation, clinical evidence evaluating integrated laser, injectable, and topical treatment protocols remains limited. In particular, data addressing epidermal barrier function and objective skin quality parameters are scarce. To date, no prospective study has evaluated the combined use of non-ablative fractional laser therapy, CaHA-HA injectable biostimulation, and adjunctive topical cosmeceuticals as an integrated protocol simultaneously targeting both pigmentation and epidermal barrier function. Accordingly, the primary aim of this prospective pilot study was to evaluate the efficacy and safety of a combined treatment protocol incorporating accelerated non-ablative fractional diode laser therapy, injectable non-cross-linked calcium hydroxyapatite-hyaluronic acid, and adjunctive topical retinoid and ascorbic acid in patients with skin hyperpigmentation. Secondary objectives included assessment of changes in epidermal barrier function, as measured by transepidermal water loss, as well as evaluation of skin texture, overall skin quality, and treatment tolerability.

MATERIALS AND METHODS

Study Design

This prospective, open-label, non-randomised, single-arm exploratory pilot study evaluated the efficacy and safety of a combined multimodal treatment protocol for facial hyperpigmentation over a 12-week follow-up period.

The study was conducted in accordance with the principles of the Declaration of Helsinki. All participants provided written informed consent prior to enrolment. Given the pilot nature of the study and the small sample size, the investigation was designed as a hypothesis-generating rather than confirmatory study. Participants were assessed at baseline and at weeks 2, 4, 6, and 12.

Participants

Five adult participants (male and female) aged 18-65 years with Fitzpatrick skin types I-IV and clinically evident facial hyperpigmentation were enrolled. Eligible diagnoses included melasma, post-inflammatory hyperpigmentation, age-related pigmentation, and photodamage-associated dyschromia. Pigmentation severity at inclusion was assessed clinically using the modified Melasma Area and Severity Index (mMASI), combined with physician evaluation of pigmentation extent, darkness, and distribution across the four standard

facial regions. Participants with a baseline mMASI score consistent with mild-to-moderate or moderate-to-severe involvement were eligible.

Inclusion Criteria:

- Age 18-65 years;
- Fitzpatrick skin types I-IV;
- Clinical evidence of mild-to-moderate or moderate-to-severe facial hyperpigmentation, assessed by the treating physician using the mMASI scoring system in conjunction with visual evaluation of pigmentation extent, darkness, and distribution (23);
- Willingness to comply with study procedures and follow-up schedule;
- Ability to provide written informed consent.

Exclusion Criteria:

- History of hypersensitivity to hyaluronic acid or laser therapy;
- Active cutaneous infection or inflammatory dermatoses;
- Pregnancy or breastfeeding;
- Prior pigmentation treatments within 6 months;
- Systemic conditions contraindicating laser or injectable therapy;
- Use of medications affecting pigmentation (e.g., corticosteroids);
- Clinical or historical evidence of pigmentary disorder with distinct aetiology precluding mMASI-based assessment (e.g., lichen planus pigmentosus, naevus of Hori, naevus of Ota).

Four enrolled participants completed the study without protocol deviations. One minor protocol deviation was noted (self-applied semi-permanent lip colour in Case 1), which did not affect the assessment zones or study outcomes.

Interventions

Participants underwent a standardised multimodal treatment protocol combining laser therapy, injectable biostimulation, and topical cosmeceutical therapy.

Accelerated Non-Ablative Fractional Diode Laser

Non-ablative fractional laser treatments were performed using a 1470-nm diode laser system (LaserMe; Berger & Kraft Medical Sp. z o.o., Poland). The device operates in fractional, non-ablative contact mode, delivering multi-millisecond pulses with constant beam power. Energy density is adjustable between 5 and 50 mJ per treatment point, with inter-spot spacing selectable from 1.0 to 4.0 mm. The maximum output power of the diode source is 2 W.

Participants underwent accelerated non-ablative fractional diode laser sessions at weeks 0, 2, and 4. Treatment parameters were individualised according to Fitzpatrick skin type, pigmentation severity, and clinical response, with conservative initial settings employed to minimise the risk of adverse effects. The accelerated protocol was selected to enhance cumulative dermal stimulation within a condensed treatment period while preserving epidermal integrity.

Fractional photothermolysis was used to promote epidermal turnover, melanin redistribution, and dermal collagen remodelling, mechanisms that may contribute to improved optical skin properties and reduced visual prominence of hyperpigmented lesions (9, 11). Energy titration was performed conservatively to limit inflammatory responses, which are known to exacerbate dyschromia, particularly in individuals with Fitzpatrick skin types III-IV.

Injectable Therapy

A biostimulatory injectable formulation consisting of non-cross-linked hyaluronic acid (18 mg/mL) combined with 0.01% calcium hydroxyapatite (Neauvia Hydro Deluxe; Matex Lab, Switzerland) was administered at weeks 0 and 4. Injection volumes ranged from 1.0 to 2.5 mL per session and were distributed across areas affected by hyperpigmentation and clinically evident dermal dehydration. Injections were performed using a 30G needle via a superficial microdroplet and linear threading technique, targeting the superficial-to-mid dermis depending on anatomical location and the degree of clinically evident dermal dehydration. Treatment endpoints included homogeneous dermal hydration without visible volumetric overcorrection. No augmentation approach was employed. Post-procedure cooling and photoprotection instructions were standardised across all participants. No topical anaesthesia was required, as the procedures were well tolerated under conservative treatment parameters.

Topical Cosmeceutical Therapy

All participants followed a standardised topical regimen using medical-grade cosmeceuticals (Neauvia), initiated on Day 0 and continued for 28 days. A retinoid-based formulation (Neauvia Retinoids Concentrate Serum) was applied on alternate evenings to promote epidermal renewal and facilitate melanin elimination. A stabilised ascorbic acid serum (Neauvia C-Shot Serum) was applied once daily in the morning to provide antioxidant support and depigmenting activity. Broad-spectrum SPF 50 sunscreen (Neauvia Photo-Defense) was applied daily and was mandatory throughout the treatment and follow-up period.

Outcome Measures

Primary Outcome

The primary outcome was change in pigmentation severity from baseline to week 12, assessed using the modified Melasma Area and Severity Index (mMASI) as described by Pandya et al. (23). The mMASI is a validated clinician-rated scoring system that quantifies the area of melasma involvement and darkness level across four facial regions (forehead, right malar, left malar, and chin), yielding a composite score ranging from 0 (no involvement) to 24 (maximum severity). The mMASI was selected over the original MASI as it excludes the homogeneity component, which has been shown to have poor inter-rater reliability (23). Although originally developed and validated for melasma, the mMASI has been adopted in published studies as a pragmatic semi-quantitative tool for the assessment of facial pigmentation severity beyond melasma, given the absence of a universally validated scoring instrument for all pigmentary disorders (3, 24). In this pilot study, the mMASI was applied as a reproducible and clinician-familiar scoring framework rather than as a disease-specific diagnostic instrument. The score was administered consistently across all visits by the same investigator to minimise inter-observer variability, and was used in conjunction with standardised clinical photography and TEWL measurement to ensure multidimensional outcome assessment. Assessments were performed at baseline and at weeks 2, 4, 6, and 12.

Secondary Outcomes

Skin hydration and barrier function

Transepidermal water loss (TEWL) was measured at baseline and week 12 in accordance with the guidelines established by the European Expert Group on Efficacy Measurement of Cosmetics and Other Topical Products (EEMCO) (25). Measurements were obtained at the forehead under standardised environmental conditions (ambient temperature 20 ± 1 °C, relative humidity 40-60%). Participants acclimatised for a minimum of 20 minutes prior to measurement. A calibrated evaporimetry probe was applied to the skin surface for

approximately 30 seconds per reading, and the mean of three to five consecutive readings was recorded as the representative TEWL value for each participant at each time point. Elevated TEWL values indicate impaired epidermal barrier function.

Photographic assessment

Standardised high-resolution clinical photographs were obtained at baseline and at each follow-up visit under consistent lighting conditions. Blinded visual comparison of serial images was performed to evaluate changes in pigmentation intensity, skin tone uniformity, and overall skin appearance.

Safety and tolerability

Adverse events were monitored and documented at every study visit. Events were classified by type, severity (mild, moderate, or severe), and resolution. Severity grading was based on clinical physician assessment: mild events were defined as transient and requiring no intervention; moderate events as those causing noticeable discomfort or requiring symptomatic management; and severe events as those causing significant functional impairment or requiring medical intervention.

RESULTS

Study Population and Follow-up

Five participants were enrolled in the study, and all completed the full 12-week follow-up period. Attendance was complete at all scheduled visits, including baseline and weeks 2, 4, 6, and 12. No withdrawals or missing data were recorded. One minor protocol deviation was noted (self-applied semi-permanent lip colour in Case 1), which did not affect the assessment zones or study outcomes. Baseline pigmentation severity ranged from mild-moderate to severe. Individual baseline characteristics and patterns of clinical response are presented in Table I.

Table I. *Baseline Characteristics and Clinical Response by Participant.*

Case	Fitzpatrick Skin Type	Baseline Pigmentation Severity	Baseline mMASI	Week 12 mMASI	Reduction (%)	Time to First Visible Improvement	Clinical Outcome at Week 12
1	II	Moderate	13	5	61.5%	Week 4	Marked improvement
2	I	Moderate	13	5	61.5%	Week 6	Marked improvement
3	III	Severe	16	10	37.5%	Week 6	Moderate improvement
4	II	Mild-Moderate	12	7	41.7%	Week 6	Moderate improvement
5	II	Severe	16	8	50.0%	Week 6	Marked improvement

MASI, modified Melasma Area and Severity Index.

Outcome Measures

Primary Outcome

A reduction in mMASI scores was observed in all participants from baseline to week 12. Mean mMASI scores decreased from 14.0 (range 12-16) at baseline to 7.0 (range 5-10) at week 12, corresponding to a mean of individual percentage reductions of 50.4% (Figure 1).

One participant (Case 1) exhibited visible clinical improvement by week 4; in the remaining participants, the first observable changes were noted at week 6. By week 12, all participants demonstrated sustained reduction in pigmentation severity compared with baseline.

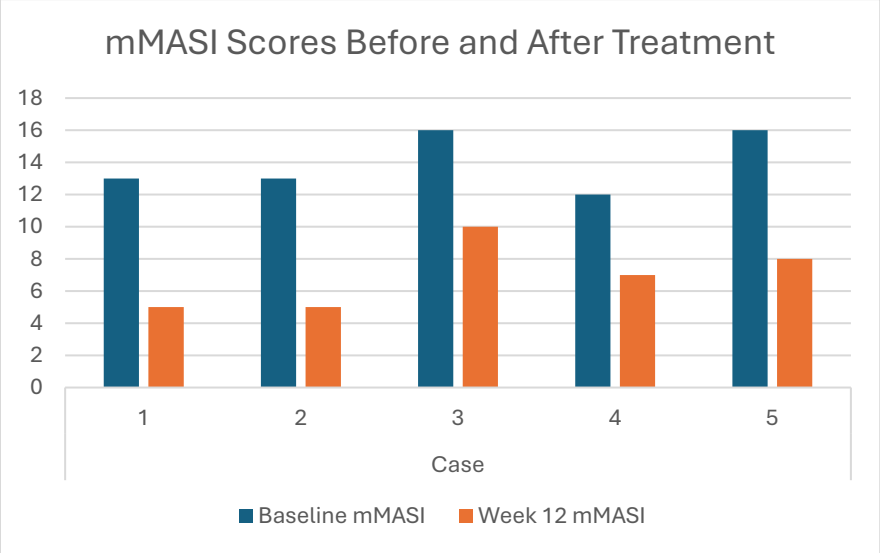

Figure 1. *Individual mMASI Scores at Baseline (Week 0) and Week 12 Following Combined Laser-Injectable-Topical Treatment.*

Secondary Outcomes

Skin Hydration and Barrier Function

Four of five participants demonstrated a reduction in TEWL at week 12 compared with baseline, indicating improvement in epidermal barrier function. Mean TEWL values decreased from 19.0 g/m²/h (SD 3.2; range 14.0-22.0) at baseline to 14.4 g/m²/h (SD 1.1; range 13.0-16.0) at week 12. One participant (Case 5), who presented with normal baseline TEWL values, exhibited stable measurements throughout the study period. The largest absolute reduction was observed in Case 1 (−9.0 g/m²/h), who also demonstrated the greatest clinical improvement in pigmentation severity. Individual TEWL values are presented in Table II.

Table II. *Individual Transepidermal Water Loss (TEWL) Values at Baseline and Week 12.*

Case	Baseline TEWL (g/m²/h)	Week 12 TEWL (g/m²/h)	Change (g/m²/h)	Interpretation
1	22.0	13.0	−9.0	Marked improvement
2	20.0	15.0	−5.0	Improved
3	18.0	14.0	−4.0	Improved
4	21.0	16.0	−5.0	Improved
5	14.0	14.0	0.0	Stable (normal baseline)
Mean (SD)	**19.0 (3.2)**	**14.4 (1.1)**	**−4.6**	—

Photographic Assessment

Standardised high-resolution clinical photographs demonstrated visible lightening of hyperpigmented areas in all participants by week 12. Improvements in skin tone uniformity and overall skin appearance were apparent by week 6 and were maintained at the final follow-up visit. Photographic findings were consistent

with clinical pigmentation scores and TEWL measurements. Representative before-and-after images are shown in Figure 2.

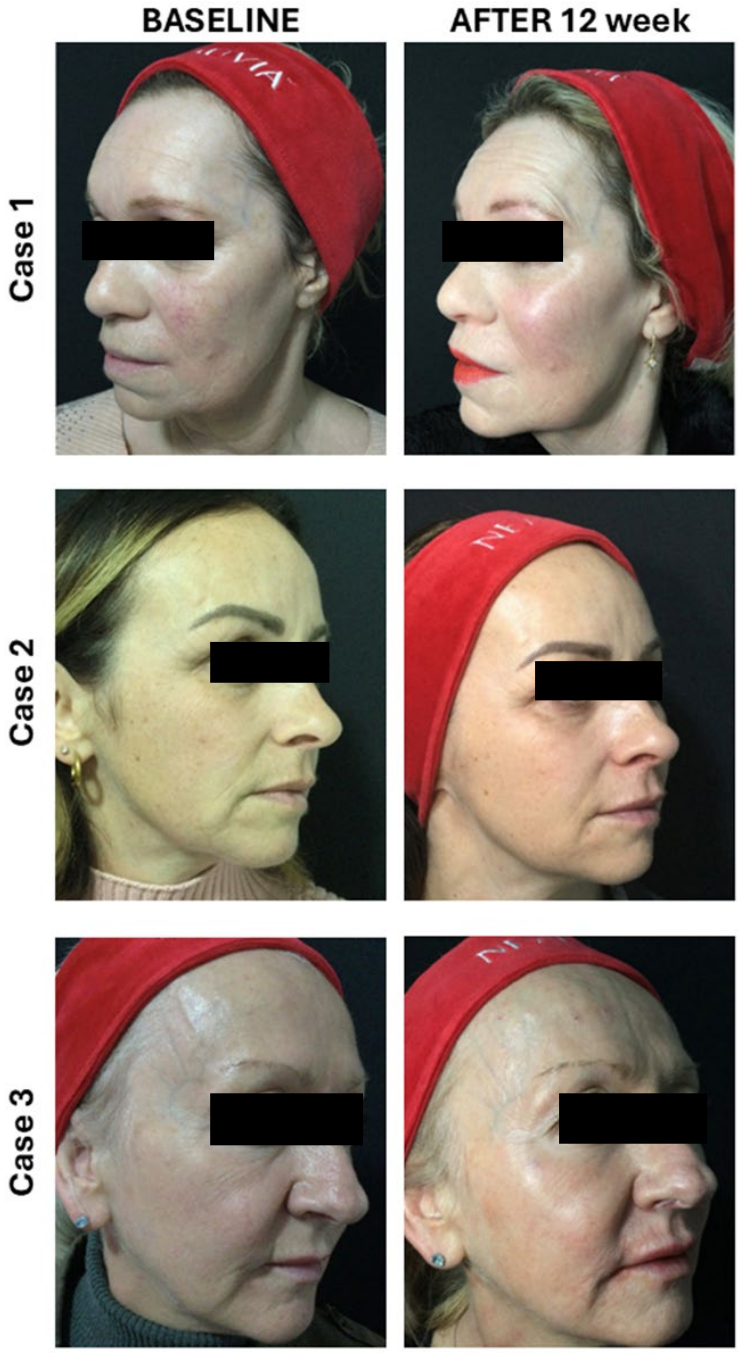

Figure 2. *Standardised clinical photographs of Cases 1-3 at baseline (week 0) and week 12 following combined laser-injectable-topical treatment. All three participants demonstrate visible reduction in facial hyperpigmentation, improved skin tone uniformity, and enhanced overall skin quality at week 12 compared with baseline. Photographs were taken under standardised conditions with consistent lighting, positioning, and camera distance. Images are presented with participant consent. mMASI assessment was performed across the forehead, malar regions, and chin in accordance with the standard scoring protocol.*

Safety and Tolerability

The combined treatment protocol was well tolerated. No serious adverse events were reported. Mild and transient adverse events included erythema (n = 2), mild swelling at the treatment or injection sites (n = 2), and minor bruising (n = 1). All adverse events resolved spontaneously without intervention. No burns, scarring, worsening of pigmentation, or treatment-related discontinuations were observed (Table III).

Table III. *Adverse Events Summary.*

Adverse Event	Number of Cases (n=5)	Severity	Resolution
Erythema	2	Mild	Spontaneous
Swelling	2	Mild	Spontaneous
Bruising	1	Mild	Spontaneous
Burns	0	—	—
Serious adverse events	0	—	—

DISCUSSION

This prospective pilot study provides preliminary evidence that a multimodal protocol combining non-ablative fractional laser therapy, injectable biostimulatory agents, and adjunctive topical therapy may safely and consistently improve hyperpigmentation severity, skin texture, and epidermal barrier function. Importantly, clinical improvement was observed not only in pigment intensity but also in transepidermal water loss, suggesting restoration of broader skin homeostasis rather than isolated depigmentation (4-5, 7-8). The mean mMASI reduction of 50.4% (mean of individual percentage reductions) observed in the current study is consistent with the upper range of reductions reported for laser monotherapy in published series (17-50%, depending on laser type, number of sessions, and patient phototype (26)), and exceeds reductions typically reported for topical retinoid monotherapy (37-41% over 14 weeks (18)) or topical ascorbic acid alone, which has demonstrated only modest and delayed depigmenting effects as a sole agent (27). These observations suggest that the multimodal approach may confer additive clinical benefit beyond what individual components achieve in isolation.

The non-ablative fractional diode laser component likely contributed to early pigment lightening through enhanced epidermal turnover and redistribution of melanin, as well as to later improvement via dermal remodelling. Fractional photothermolysis induces controlled microthermal zones that stimulate cytokine-mediated repair pathways while preserving surrounding tissue, thereby limiting widespread inflammation, a key consideration in pigment-prone skin (9-12). This mechanism is particularly relevant in melasma and other hyperpigmentation disorders, which are increasingly recognised as inflammatory and photoaging-related conditions rather than purely melanocytic abnormalities (4, 5).

Injectable non-crosslinked calcium hydroxyapatite-hyaluronic acid (CaHA-HA) may have augmented and prolonged clinical outcomes by improving dermal hydration, extracellular matrix support, and fibroblast activation. Calcium hydroxyapatite has been shown to stimulate neocollagenesis and dermal remodelling, while hyaluronic acid enhances tissue hydration and elasticity, contributing to improved skin quality and reduced TEWL (14-17). The observed association between reductions in TEWL and improvements in pigmentation severity in this study supports emerging evidence that epidermal barrier integrity and dermal support play a central role in pigment stability and relapse prevention (7, 8). Notably, Case 5, who demonstrated no change in TEWL, had a near-normal baseline value of 14.0 g/m²/h, consistent with a floor effect; the absence of measurable improvement in this participant likely reflects pre-existing adequate barrier function rather than treatment failure.

Adjunctive topical retinoid therapy likely enhanced epidermal renewal and facilitated melanin elimination by modulating keratinocyte differentiation and melanosome transfer, consistent with the established literature (18, 19). Ascorbic acid provided antioxidant protection, inhibition of melanogenesis, and support for collagen synthesis, while also mitigating oxidative stress induced by laser procedures, potentially improving procedural tolerability and recovery (20-22). Mandatory photoprotection was essential in preventing ultraviolet-induced relapse, which remains a major contributor to treatment resistance and recurrence in melasma and related pigmentary disorders (1-3, 5).

Notably, no cases of post-inflammatory hyperpigmentation or pigment worsening were observed. This finding underscores the safety of a conservative, layered treatment strategy that prioritises epidermal barrier preservation and dermal support. Such an approach is particularly relevant given the increased risk of pigmentary complications associated with aggressive monotherapies and excessive thermal injury, especially in patients with Fitzpatrick skin types II-IV (12).

Several limitations should be acknowledged. These include a small sample size, an open-label design, a short follow-up period, and the absence of a control or comparator arm. Assessments were performed by the treating clinician without independent blinded evaluation, and no randomisation was employed, limiting the ability to draw causal inferences. Objective pigment quantification methods such as colorimetry, dermoscopy, or reflectance confocal microscopy were not employed, and the relative contribution of each individual treatment component cannot be isolated. The absence of a single-modality comparator arm prevents direct attribution of outcomes to any specific intervention. Additionally, the study population was limited to Fitzpatrick skin types I-IV, and findings may not be generalisable to all patient populations. Nevertheless, as a hypothesis-generating pilot study, these findings provide a rationale for larger, randomised controlled trials incorporating longer follow-up periods, independent blinded outcome assessors, objective biophysical measurements, and standardised pigmentation scoring systems.

CONCLUSION

In this prospective pilot study, a combined protocol integrating accelerated non-ablative fractional diode laser therapy, injectable non-cross-linked calcium hydroxyapatite-hyaluronic acid, and adjunctive topical retinoid and ascorbic acid demonstrated a favourable safety profile and consistent clinical improvement in hyperpigmentation severity, skin texture, and epidermal barrier function over a 12-week period. These findings support a shift toward multimodal, skin-quality-focused treatment paradigms for pigmentary disorders and warrant further investigation in controlled clinical trials.

Ethics Statement: The study was conducted in accordance with the principles of the Declaration of Helsinki. All participants provided written informed consent prior to enrolment. This work constitutes a prospective clinical evaluation of treatments administered as part of routine aesthetic practice using CE-marked devices and approved products within their licensed indications. In accordance with the criteria established by the UK Health Research Authority (HRA), the project was classified as a service evaluation rather than a clinical research study and therefore did not require submission to a Research Ethics Committee or HRA Approval. All data were collected and handled in accordance with applicable data protection legislation.

Conflict of Interest: The authors declare no conflicts of interest.

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