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A Topical Depigmentation Program Against Hyperpigmentation Enhances the Benefits of Previously Performed Chemical Peeling Procedures of the Face

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Synopsis

Chemical peeling can reduce skin hyperpigmentation; however, once exhausted its thinning action, the depigmentation process does not continue further. We carried out a monocentric, prospective, noncontrolled study aimed at the evaluation of the efficacy, safety, ease of use, pleasantness, and tolerability of a depigmentation topical treatment program in women submitted to a previous chemical peeling. The topical treatment has been administered daily for 30 days to 16 women submitted to a chemical peeling containing a fixed-dose combination of salicylic acid, pyruvic acid, and retinoic acid within 7 days before study inclusion. Target skin areas have been evaluated for melanin concentration and skin texture before peeling and at study visits 1 (after peeling) and 2 (after the 30-day treatment). The topical treatment program induced a decrease in melanin concentration between study visits 1 and 2 (–4.74%; $p = 0.0008$). It reduced melanin concentration even further between the prepeeling period and visit 2 (–7.8%; $p < 0.0001$). Patients rated the depigmentation topical treatment program as "very simple" (87.5%) and "simple" (12.5%) to use and as "pleasant" (56.25%) and "very pleasant" (43.75%). Results support the use of the home-based depigmentation topical treatment program to potentiate the effectiveness of a previous chemical peeling in hyperpigmentation reduction.

INTRODUCTION

Cutaneous pigment disorders can affect both genders, with prevalence among female subjects, and with different etiology. Pigment disorders can cause an aesthetic discomfort that, in many cases, is quite relevant, representing a persistent psychosocial burden for the patient (1). Hyperpigmentation consists of localized dark skin patches caused by qualitative and quantitative alterations in pigment distribution. Cutaneous pigment disorders can be classified as hypermelanosis, that is, an increased or altered distribution of the pigment melanin in the epidermis and/or dermis, and as endogenous or exogenous hyperchromia (e.g., due to accumulation of nonmelanin pigments, such as hemosiderin, a granular pigment derived from ferritin; bilirubin, an orange–yellow pigment normally

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occurring during heme catabolism; drugs; etc.). Acquired forms of hypermelanosis can have several different causes (e.g., metabolic or endocrine disorders, deficiencies, cutaneous injuries, inflammatory dermatoses, and systemic and neurological diseases) (2,3). Melasma is the most frequent form of acquired hypermelanosis, occurring most commonly on the face and also in extrafacial areas (4), and is characterized by an increased deposition of melanin (5). Various epidemiological studies estimated the prevalence of melasma at 1% in the general population and 9–50% in higher risk populations (6,7). Morphologically, melasma presents as symmetric reticulated hyperpigmented patches with irregular borders on the centrofacial region, malar cheeks, mandible, and rarely upper chest and extremities (4). Melasma, rather than a rigid linear epidermal problem, is now considered a heterogeneous pathology derived from a complex interplay among melanocytes, keratinocytes, dermal fibroblasts, and vascular endothelial cells (8). Melanin is produced by melanocytes in the basal layer of the epidermis from the amino acid tyrosine, within organelles known as melanosomes, through a reaction catalyzed by the tyrosinase enzyme. Melanocytes then export mature melanosomes to nearby keratinocytes through their dendrites to induce pigmentation (9). Immunohistochemical studies on skin biopsies confirmed a significant increase in melanin in melasma but no quantitative increase in melanocytes in the hyperpigmented areas of skin that, however, resulted in larger and very prominent dendrites (10). The factors that can cause an increase in melanin concentration are numerous and include, among others, hormonal and genetic factors, high exposure to ultraviolet rays, darker skin types, some drugs, infections, or inflammatory processes (6,7). However, the pathogenesis of melasma is not yet fully understood. Increased expression of the stem cell factor in the dermis and of the tyrosine kinase receptor c-kit in the epidermis has been suggested to play an important role in the mechanism of hyperpigmentation in melasma (11). A relevant role in melasma has also been suggested for increased microcirculation, triggered by a significantly increased level of the vascular endothelial growth factor (VEGF), a major angiogenic factor of the skin constitutively produced by keratinocytes and whose receptors are expressed both in melanocytes and vascular endothelial cells (12,13). The VEGF could have a direct influence on melanocyte behavior and melanogenesis through its receptors. Interestingly, the VEGF is known to stimulate the arachidonic acid release and the phosphorylation and activation of the cytosolic phospholipase A2 (14). It is possible that the resulting metabolites from this pathway affect melanogenesis as well.

The result of increased melanin concentration is an uneven skin tone. Although common, the management of this disorder remains challenging, given the incomplete understanding of its pathogenesis, chronicity, and recurrence rates. Moreover, melasma treatment is quite challenging because of the presence of melanin deposits at varying depths in the epidermis and dermis (15), with dermal and mixed melasma (a combination of the epidermal and dermal types) having the worse prognosis because many topical therapies are not able to target dermal melanophages (16). Several methods and strategies have been reported so far in the literature to address skin hyperpigmentation. The goal of melasma treatment is to decrease melanin production and increase its elimination. In addition to traditional treatments, there are also new promising strategies, including oral, topical, and procedural therapies (5). Among them, the chemical peeling, also called "chemical resurfacing," that consists in the application of one or more substances, in immediate or delayed sequence, which causes a chemical ablation of defined skin layers. This treatment leads to a uniform and taut skin, through the regeneration and repair mechanisms of the

epidermis and dermis stimulated by a controlled inflammatory reaction, with the synthesis of new collagen and a more evenly distributed melanin (15,17). Chemical peels are effective in improving skin tone and reducing melanin concentration. However, outpatient chemical peels can be combined with other home-based treatments to provide a synergistic approach and optimize clinical outcomes, enhance patients' satisfaction, and allow clinicians to tailor the treatment to individual patient needs and conditions (15,18). In particular, Rendon et al. (15) reviewed several chemical peel protocols applied to melasma, including those based on glycolic acid and salicylic acid, and concluded that a maintenance therapy is needed when peeling is used for melasma, and that chemical peels may be most effective when used in combination with medical therapy or other procedures possibly because peels remove melanin, although other treatments inhibit melanocytes or melanogenesis.

Chemical peeling treatments can be classified into three categories: superficial peels, which exfoliate the epidermal layers without going beyond the basal layer; medium depth peels, which reach to the upper reticular dermis; deep peels, which penetrate the lower reticular dermis (18). The depth of peeling, and thus the degree of its therapeutic effects, is affected by different factors, including the properties of the chemical agents used (e.g., concentration and pH), the application technique, and the skin condition and sensitivity.

Once a chemical exfoliant has exhausted its thinning action on epidermal structures, the depigmentation process does not continue further and can be considered stabilized. However, its beneficial action could be potentiated by subsequent dermocosmetic treatments. Here, we report the results of a monocentric, prospective, noncontrolled study carried out in female subjects submitted to chemical peeling within 7 d before the study inclusion and aimed at the evaluation of the effects of a 30-d topical, depigmenting dermocosmetic treatment program on facial hyperpigmentation, pigment uniformity, and skin texture.

METHODS

STUDY DESIGN

This was a monocentric, prospective, noncontrolled study carried out between December 2018 and February 2019 (first subject enrolled and last subject completed) in Milan, Italy, aimed at the evaluation of the efficacy, safety, ease of use, pleasantness, and tolerability of a depigmenting topical dermocosmetic treatment program in the reduction of facial hyperpigmentation, measured as dark spot size reduction, in subjects submitted to chemical peeling within 7 d before the study inclusion.

The protocol, consent form, information sheet, and any written information to be provided to study participants were submitted to an independent ethics committee, and a copy of the written approval was obtained. The study was conducted in accordance with the Italian regulations and requirements.

INCLUSION CRITERIA

The study inclusion criteria were signed informed consent, ≥18 years of age, a good general health condition, and superficial depigmenting chemical peeling treatment within 7 d before the study enrollment with the Definisse™ Peel Program (Mastelli Srl, Sanremo, Italy).

The Definisse Peel Program includes a fixed-dose combination of salicylic acid, pyruvic acid, and retinoic acid, with the integration of the depigmentation agents Lumiskin™ (diacetyl boldine, a tyrosinase inhibitor) (Sederma, Le Perray-en-Yvelines, France) and SEPIWHITE™, containing lipoaminoacid (undecylenoyl phenylalanine) (Seppic SA, Paris, France).

EXCLUSION CRITERIA

The study exclusion criteria were pregnancy; delivery during the last 30 d; current inflammatory and infective skin diseases; current topical facial treatment with exfoliating, depigmenting products or topical/systemic use of antibiotics and photosensitizing drugs; skin phototypes IV-V according to Fitzpatrick classification; cognitive impairment or any other condition or a condition that, according to the investigators, made possible a poor adherence to required procedures planned for the entire study duration; any disease or skin condition or other body condition that, according to investigators' judgment, could place the subject at risk if participating in this study or might interfere with study assessments; skin exposure planned during the study period or exposure to ultraviolet rays or use of self-tanning products; known intolerance to one or more components of the investigational products; and prior participation in this study.

PANEL COMPOSITION

In this clinical study, 20 women with acquired hyperpigmentation who had undergone a chemical peeling treatment with a superficial chemical peel (Definisse Peel Program) including a fixed-dose combination of salicylic acid, pyruvic acid, and retinoic acid for facial skin defects such as melasma, skin spots, postinflammatory hyperpigmentation, photoaging, and chronoaging were evaluated for enrollment. No sample size calculation was performed. The investigator obtained the informed consent from each patient before the inclusion in the study, in accordance with the International Conference on Harmonisation-Good Clinical Practice Guidelines and the Declaration of Helsinki. Sixteen of the 20 women satisfied both the protocol inclusion and exclusion criteria described previously and were selected for study participation (mean age: 53 years, range: 23–77 years). Patients' demographic data are summarized in Table I.

PROTOCOL

At study visit 1, after eligibility confirmation, all patients received the hyperpigmentation topical treatment program products to start the home-based treatment immediately. The study participants were instructed to apply at home the study products every day for 30 d, as detailed in the "Products" section. After that, a final visit (end of treatment/end of the study) was performed 30 d later (visit 2).

Pregnancy tests and clinical analysis were performed for participants of childbearing potential or to check that their medical history did fit the inclusion/exclusion criteria (Table I). All the subjects attended two study visits: initial visit-T0-day 1 (visit 1) and final visit-T1-day 31 (visit 2). The products in this open-label study were applied daily from day 1 to day 30. During study visit 1, the written consent for study participation and personal data processing was obtained, and data collection and tests were initiated to

Table I
Patients' Demographic Data and Baseline Values for Skin Parameters

Parameter	Statistics/categories	Pigment solution ($N = 29$)
Age (years)	*N*	16
	Mean (SD)	52.75 (11.40)
	Median	51.00
	Minimum/maximum	28.00/77.00
Medical history [*N* (%)]	No	9 (56.25%)
	Yes	7 (43.75%)
Product used for peeling [*N* (%)]	Lightening peel	16 (100.0%)
Pregnancy test [*N* (%)]	No	9 (56.25%)
	Yes	7 (43.75%)
	Negative	7 (100.0%)
Melanin concentration	*N*	16
	Mean (SD)	0.62 (0.07)
	Median	0.64
	Minimum/maximum	0.50/0.74
Skin texture	*N*	16
	Mean (SD)	11.17 (3.82)
	Median	10.8
	Minimum/maximum	6.62/20.29
Pigment uniformity	*N*	16
	Mean (SD)	0.05 (0.01)
	Median	0.05
	Minimum/maximum	0.03/0.08

verify the fulfillment of the study inclusion/exclusion criteria listed previously. A clinical and instrumental evaluation of skin quality and degree of skin pigmentation using the digital analysis of cutaneous surface (DACS) was performed.

During study visit 2, the following procedures were completed for each study subject: clinical and DACS-mediated evaluation of skin quality and degree of skin pigmentation; recording of any changes in concomitant treatments; recording of any adverse event (AE) or serious AE (SAE), with particular attention to those that could have occurred in the treated areas (e.g., burning, redness, and itching); collection of unused (or partially used) study products and verification of their use made by the subjects; completion by the investigator of the questionnaire on treatment satisfaction; and compilation by the subjects of the questionnaires on treatment satisfaction and on the pleasantness and ease of use of the hyperpigmentation topical treatment program.

The 16 study participants were sufficiently compliant with the prescribed treatments, and none of them dropped out prematurely. No AEs or SAEs were reported during the study. Local tolerability of the three components of the hyperpigmentation topical treatment program was assessed by the study investigators, and no safety concern was issued.

Primary study end points were hyperpigmentation reduction and change in skin texture induced by the investigational product applied for 30 d after a chemical peeling. The reduction of hyperpigmentation and the changes in skin texture were assessed by instrumental tests (DACS), described in more detail in the following texts (19–22). Because the study product was intended for at-home administration, the study included as secondary end points the ease of use of the treatment, its pleasantness, the overall satisfaction of patients and study investigators, and the safety and tolerability of the treatment.

PRODUCTS

The hyperpigmentation topical treatment program (Pigment Solution™ Program, Relife S.r.l., Florence, Italy) is a cosmetic treatment specifically formulated to reduce hyperpigmentation and achieve a uniform skin tone. It consists of three products: (i) a preparation cleanser—a mild detergent, containing a mixture of soothing ingredients, formulated to cleanse and prepare the skin for treatment, facilitating dermal penetration of depigmenting agents; (ii) a day cream (kojic acid 0.3%, vitamin E 0.05%, vitamin A 0.005%, and AQUAXYL™ complex 3%) (Seppic SA); (iii) a night cream (kojic acid 0.3%, glycolic acid 5.7%, AQUAXYL complex 3%, and scrubbing beads 1.5%).

The treatment was administered at home. All patients were instructed to apply the products every day for 30 consecutive days. Subjects had to apply the day cream in the morning (two fingertips of cream on the whole face) and the night cream in the evening (two fingertips of cream on the whole face), massaging with circular movements in the areas affected by hyperpigmentation (sun spots, age spots, and photosensitivity spots). A fingertip unit corresponds to about 0.43 g of cream for a female adult. Subjects had to prepare the skin using the preparation cleanser before each application (2 mL of cleanser on the whole face, 1 mL in the morning, 1 mL in the evening, massaged for 2 min, and then rinsed with water). No increase or reduction in daily applications was allowed. The study products were supplied by the study Sponsor Relife S.r.l.

The superficial chemical peeling/depigmentation treatment given within 7 d before the study enrollment included a fixed-dose combination of salicylic acid, pyruvic acid, and retinoic acid, with the integration of the depigmentation agents Lumiskin (diacetyl boldine, a tyrosinase inhibitor) and SEPIWHITE, containing lipoaminoacid (undecylenoyl phenylalanine) acting as a selective antagonist of α-melanocyte-stimulating hormones, involved in the regulation of melanogenesis.

DACSs

The total amount of melanin, pigment uniformity, and the skin texture in target skin areas of each subject were assessed using the Antera 3D® system (Miravex Limited, Dublin, Ireland), an objective, reliable, fast, noninvasive, nonpainful tool for DACS based on the use of multispectral sources and on the 3D mapping of the skin surface. In more detail, the Antera 3D camera produces a multidirectional light beam by emitting diodes of seven different light wavelengths, spanning the entire visible spectrum. The camera collects the reflected light and uses the reflection angle to produce a 3D reconstruction of the skin surface. This reconstruction is based on shape from shading, extensively modified to eliminate skin glare and improve the accuracy of measured data. The reflectance data are transformed into skin absorption coefficients and used to quantify melanin concentration using the mathematical correlation with known spectral absorption data of this chromophore.

Target skin areas were photographed with the Antera 3D camera (field of view: 56 × 56 mm; resolution: 0.1 mm; 3D depth resolution: 0.01 mm; accuracy: ±5%). Associated Antera 3D software allows the analysis of the skin in 2D and 3D, together with a multispectral analysis of epidermis and dermis pigmentation. The Antera 3D software allows the operator to select the investigated skin area, which is automatically recognized during the

subsequent acquisitions. An algorithm is then used to analyze the skin surface and measure parameter changes versus baseline values.

PRIMARY STUDY END POINTS

Skin hyperpigmentation and texture were the primary efficacy end points assessed in the study. A comparison between melanin concentration, pigment uniformity, and parameters inherent to the skin texture before and after the study treatment was made.

SECONDARY STUDY END POINTS

Ease of use of the treatment. The ease of use of the hyperpigmentation topical treatment program was assessed through a five-point questionnaire, where 1 = very simple, 2 = simple, 3 = neither simple nor complicated, 4 = complicated, and 5 = very complicated. The patients completed the questionnaires at the end of the study (visit 2).

Pleasantness of the treatment. The pleasantness of the three products constituting the hyperpigmentation topical treatment program was assessed through three five-point questionnaires (one per product), where 1 = very pleasant, 2 = pleasant, 3 = neither pleasant nor unpleasant, 4 = unpleasant, and 5 = very unpleasant. The patients completed the questionnaires at the end of the study (visit 2).

Overall satisfaction. The investigator and the patients' satisfaction with regard to the results obtained after the treatment was assessed through two separate five-point questionnaires, where 1 = very satisfied, 2 = satisfied, 3 = neither satisfied nor dissatisfied, 4 = not satisfied, and 5 = very dissatisfied. The investigator and the patients completed the questionnaires at the end of the study (visit 2).

Safety and tolerability of the treatment. The safety profile of the hyperpigmentation topical treatment program was assessed in terms of the number of AEs reported by the subjects or detected by the investigator. All the patients who received at least one application of one of the three products of the hyperpigmentation topical treatment program were included in the safety analysis. AEs were coded using the Medical Dictionary for Regulatory Activities. The number of patients who experienced at least one AE, an AE related to the product, an SAE and the number of subjects withdrawn because of an AE are summarized.

STATISTICAL ANALYSIS

Data were analyzed using an intention-to-treat approach. The statistical analysis was carried out on patients who had completed study visits 1 and 2 ($n = 16$). Data were expressed as average, median, standard deviation, range for continuous variables, and as number of subjects and percentage values for categorical variables. *T*-tests for paired data were performed to assess whether changes versus the initial visits were statistically significant. The significance level of the statistical tests used was 5%; the statistical tests that gave p values lower than 0.05 were considered statistically significant. Where appropriate, 95% confidence interval was calculated. Missing data were not replaced. Data were analyzed with SAS 9.4 software for Windows (SAS Institute Inc., Cary, NC).

ETHICS

The clinical study was conducted in accordance with the ethical principles reported in the Declaration of Helsinki as amended by the World Medical Association in Fortaleza in 2013, in accordance with the Good Clinical Practice Guidelines and in compliance with Italian laws and regulations, including the General Data Protection Regulation and the Italian D.Lgs. 101/2018.

RESULTS

The study investigators assessed through the DACS the individual skin parameters (melanin concentration, pigment uniformity, and skin texture) at baseline (during study visit 1) and at the end of treatment (study visit 2). Individual data for skin parameters were available also for the prestudy period, that is, between the prepeel and study visit 1. The percentage changes in skin parameters between study visits 1 and 2 were described by mean, standard deviation, median, and minimum and maximum values. A paired *t*-test was performed to assess whether the changes versus baseline values measured at study visit 1 were statistically significant.

Baseline mean values in selected 56 × 56-mm skin areas were 0.62 for melanin concentration [standard deviation (SD) = 0.07, range: 0.50–0.74], 0.047 for pigment uniformity (SD = 0.011; range: 0.03–0.08), and 11.17 for skin texture (SD = 3.82; range: 6.62–20.29) (Table I). Prepeel mean values were 0.64 for melanin concentration (SD = 0.06, range: 0.52–0.75) and 10.80 for skin texture (SD = 4.24; range: 5.66–20.69). A comparison was made for each individual target skin area between the examination performed before and after the study treatment.

The mean melanin concentration at study visit 2 decreased to 0.59 (SD = 0.07, range: 0.48–0.70), with a mean of differences between study visits 1 and 2 of −0.03 (SD = 0.03, $p = 0.0004$). The individual measurement of melanin concentration at study visits 1 and 2 and the individual changes between the study visits ($p < 0.001$) are shown in Figure 1. The mean pigment uniformity index at study visit 2 decreased to 0.044, with a mean of differences between study visits 1 and 2 of −0.003 (SD = 0.007, $p = 0.1664$). The mean skin texture index at study visit 2 decreased to 10.43, with a mean of differences between study visits 1 and 2 of −0.74 (SD = 1.92, $p = 0.1456$). Interestingly, the mean change of melanin concentration between the prepeel period and study visit 2 (prestudy + study period) was −7.8% ($p < 0.0001$) (Figures 2 and 3).

The ease of use of the hyperpigmentation topical treatment program was rated through a five-point questionnaire completed by the patients at study visit 2. The results were reported as number and percentage of patients for each point of the questionnaire. Fourteen patients (87.50%) evaluated the treatment as "very simple to use," and two (12.50%) evaluated it as "simple to use."

The pleasantness of the three products constituting the depigmentation topical treatment program was rated through three five point-questionnaires (one per product), completed by the patients at study visit 2. The results were reported as number and percentage of patients for each point of each questionnaire. All patients rated the use of the day cream as "pleasant" (56.25%) and "very pleasant" (43.75%). Most patients rated the use of the night cream as "pleasant" (37.50%) and "very pleasant" (43.75%). Three patients (18.75%) rated the night cream use as "neither pleasant nor unpleasant" and two (12.50%)

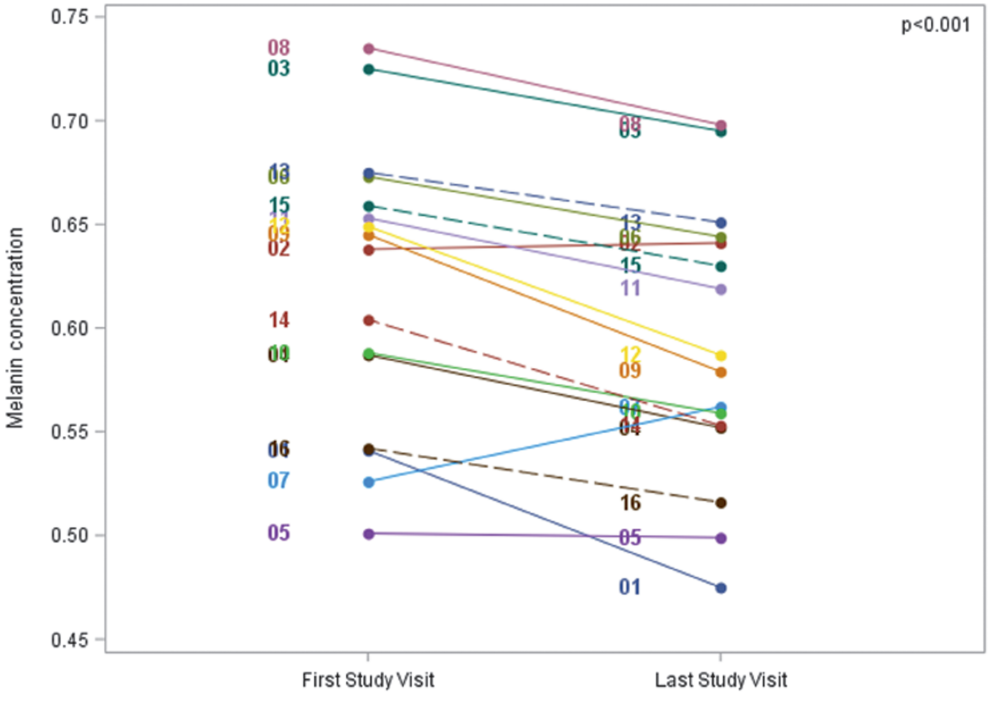

Figure 1. Assessment of the primary end point melanin concentration (%) at study visits 1 and 2, determined through the Antera 3D camera and its associated software on selected skin areas for each patient. The individual measurement of melanin concentration at study visits 1 and 2 and the individual changes between the study visits are shown. Different kinds of lines have been used in addition to different colors to help distinguish among individual changes. A p value < 0.05 was considered statistically significant.

as "unpleasant." The majority of patients evaluated the cleanser as "pleasant" (43.75%) and "very pleasant" (12.50%) (Figure 4).

The overall satisfaction of investigators and patients with the results obtained after the study treatment was assessed through two five-point questionnaires (one for the investigator and one for the patient), completed at study visit 2. The results were reported as number and percentage of patients for each point of each questionnaire. The study investigator declared to be "satisfied" (68.75%) and "very satisfied" (25%) with treatment results in the large majority of cases, with the exception of a single subject (6.25%) declaring "neither satisfied nor dissatisfied." Finally, the majority of the patients declared to be satisfied and very satisfied with the treatment results (68.75%), with the only five patients (31.25%) declaring neutral perspective as "neither satisfied nor dissatisfied" and no patients (0%) declaring dissatisfied toward the treatment result.

DISCUSSION

The subjects enrolled in this clinical study had previously received a chemical peeling/depigmentation treatment of the superficial layers of the epidermis with a product containing a fixed-dose combination of salicylic acid, pyruvic acid, and retinoic acid, with the integration of depigmentation agents able to inhibit melanin biosynthesis. Pyruvic

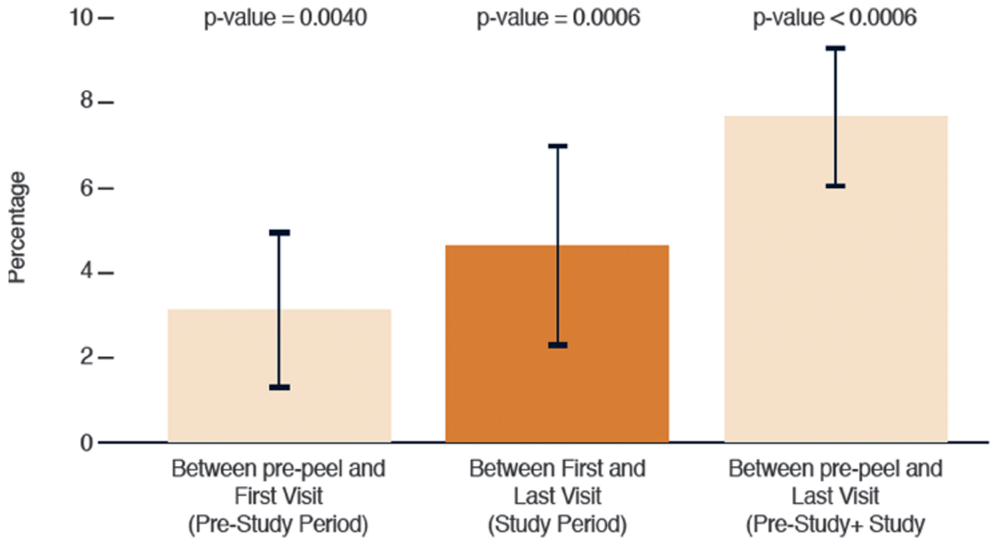

Figure 2. Reduction in melanin concentration (%) across the study steps (prestudy period, study period, prestudy + study period), determined through the Antera 3D camera and its associated software on selected skin areas for each patient. A p value < 0.05 was considered statistically significant.

acid peels have been shown to be safe and effective in treating melasma, allowing the patients to preserve their working and social life (2). Overall, our study revealed that the daily administration of the home-based hyperpigmentation topical treatment program not only maintained but also enhanced the beneficial lightening effect achieved from the previous chemical peeling, as supported by the statistically significant reduction in individual melanin concentration at study visit 2 versus visit 1 (Figure 1), and by the 2.6-fold higher melanin percent change at study visit 2 versus the prepeel period (from −3.0% to −7.8%; $p < 0.0001$) (Figure 2). These results are presumably related to the formulations of the products included in the depigmentation topical treatment program. In particular, the day cream has an adjuvant triple action: (i) promotes cell renewal, thanks to its vitamin A content; (ii) plays a lightening action and supports the inhibition of the synthesis of new melanin, thanks to kojic acid; (iii) hydrates and restructures the skin, protecting it from external agents and promotes the reduction of transepidermal water loss, thanks to the AQUAXYL complex. Of major interest, the night cream included in the depigmentation topical treatment program has a double peeling effect: it exerts both a chemical

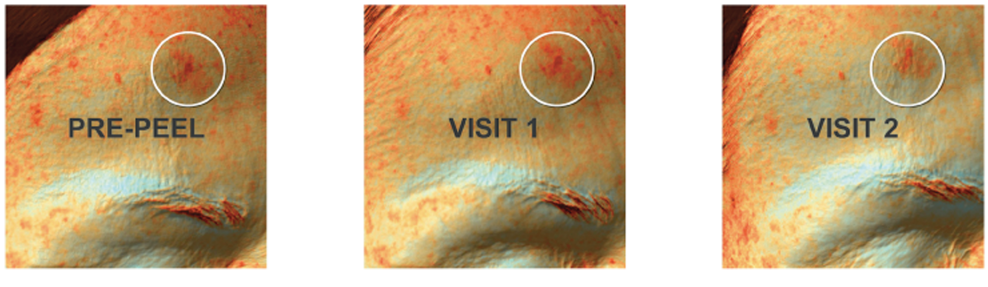

Figure 3. Antera 3D digital images showing a representative hyperpigmented patch on the skin at three different time points of the study: prepeel period; visit 1 (postpeel and study enrollment); visit 2 (end of the study).

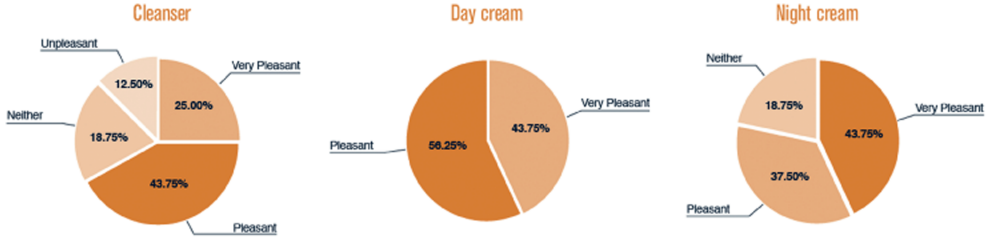

Figure 4. Pie charts showing the distribution of subjects' opinions on the pleasantness of the study products included in the depigmentation topical treatment program (including the cleanser, day cream, and night cream).

action, thanks to its glycolic acid content, and a mechanical action, thanks to the presence of squalene and scrubbing beads, specifically formulated to help uniform the skin pigmentation. The glycolic acid contained in the night cream is considered the safest and the most versatile peeling agent among all the alpha hydroxy acids used as chemical peels for the treatment of melasma because it has the smallest molecule and penetrates the epidermis the best (23). The kojic acid contained in the day and night creams is widely used for melasma treatment as well (24), and its clinically effective antimelanogenic activity on hyperpigmented skin is associated with the induction of Interleukin-6 (IL-6) production in keratinocytes (25), other than with its tyrosinase inhibition and scavenging activity of reactive oxygen species (16).

Our data revealed no statistically significant change for pigment uniformity and skin texture in the study we performed. Additional investigations with a longer study period and larger sample size will be performed to further verify an effect of the chemical peeling/depigmentation treatment we tested also on these parameters.

This study took advantage of the Antera 3D system, which proved to be a valuable, objective, easy, and reproducible method to assess the effects of a dermocosmetic treatment on hyperpigmentation, excluding any need for clinical scores (26) or self-assessment. The area selected in each patient for the study purposes showed a regular surface, without excessive concavities or convexities, potentially affecting the measurements of the selected skin parameters. Of note, a recent study compared the Antera 3D-based system with other methods (Mexameter® MX-18 and Colorimeter® CL-400, Courage+Khazaka electronic GmbH, Köln, Germany) for the skin color analysis in healthy volunteers. The Antera 3D system showed a better sensitivity and specificity and a higher repeatability versus other methods for all the parameters analyzed (22). The only intrinsic limitation of the Antera 3D system was the fixed size of the skin areas analyzed (56 × 56 mm).

Because the study product was a home-based treatment, not only its efficacy but also its safety, tolerability, ease of use, and level of patients' and physicians' satisfaction have been considered as parameters of major importance in the assessment of the hyperpigmentation topical treatment program. The treatment was safe and well-tolerated, and the satisfaction rate of investigators and patients with the overall results at study completion was very high.

Of interest, a previous multicenter, prospective study performed on 100 women affected by melasma and treated for 45 and 90 d with the same home-based depigmentation program tested in our study indicated its effectiveness on melasma even in the absence of a prestudy chemical peeling (27).

In conclusion, our data support the efficacy, safety, and tolerability of a home-based depigmentation treatment based on the combination of different ingredients and activities, leading to a potential synergic effect and enhancing the overall activity of the treatment program. Subjects' compliance with this home-based daily treatment has been assured by its ease of use and high pleasantness, as rated by the large majority of the study participants.

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