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ORIGINAL CONTRIBUTION

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Assessment of the efficacy and safety of a new complex skin cream in Asian women: A controlled clinical trial

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Summary

Background: Medical products such as hydroquinone and tretinoin have been widely used to treat various types of skin hyperpigmentation. However, these products are limited in daily use given their adverse effects. Other alternative agents with fewer adverse side effects have been developed. However, single agents often do not produce satisfactory results.

Aims: To evaluate the efficacy and safety of a new brightening complex cream containing niacinamide, tranexamic acid, oxyresveratrol, glutathione disulfide, and linoleic acid.

Patients and Methods: A total of 26 Korean women seeking to lighten their skin were enrolled. The product was applied on the face two times per day for 12 weeks. Standardized photographs were taken at baseline, 4 weeks, 8 weeks, and 12 weeks. Efficacy was assessed using melanin index (MI), erythema index (EI), and chromatic aberration values (L*, a*, and b*). Improvement perceived by investigators and patients was measured as well.

Results: The L*-value was increased at 8 weeks (0.7 ± 2.5, $P<.05$) and at 12 weeks (0.8 ± 2.5, $P<.05$). The MI was significantly decreased at 8 weeks (-4.2 ± 4.5, $P<.05$) and at 12 weeks (-3.8 ± 4.8, $P<.001$). The EI was significantly improved at 12 weeks (-3.2 ± 2.2, $P<.001$). More than 80% of patients were considered improved at 12 weeks based on the view of the investigators and patients.

Conclusions: The new brightening complex cream was proved to be effective and safe in Asian women.

KEYWORDS
Asian, skin brightening, topical cream

1 | INTRODUCTION

In Asian countries, an even and light skin tone is considered a symbol of beauty, especially among women. Common causes of skin hyperpigmentation include lentigines, melasma, and postinflammatory hyperpigmentation. Many patients are concerned about these specific hyperpigmentation disorders and generally desire a brighter skin tone in the absence of definite hyperpigmentation disorders. Cosmetic procedures, including laser treatment and chemical peeling, and topical agents are widely used.[1] However, these cosmetic procedures are expensive, time-consuming, and accompanied by the risk of side effects. Among topical agents, medical products including hydroquinone and tretinoin have been shown to be highly effective in a variety of skin hyperpigmentation disorders. However, these agents may also cause severe local reactions, prohibiting their use in general cosmetics.[2] Therefore, many other ingredients, including niacinamide, tranexamic acid, oxyresveratrol, glutathione disulfide, and linoleic acid, have been developed as alternative agents.

Yu Seok Jung and Ji Hae Lee contributed equally to this work.

However, the efficacy of a single agent is often limited. There are few clinical trials that have addressed their use. Therefore, recent efforts have been made to yield an effective combination of skin brightening agents with fewer side effects. The aim of this study was to evaluate the efficacy and safety of a new brightening complex cream in Asian women, which contains niacinamide, tranexamic acid, oxyresveratrol, glutathione disulfide, and linoleic acid.

2 | MATERIALS AND METHODS

A total of 26 Korean women were enrolled in this study. The participants were selected among those who visited the Dermatology Department of St. Vincent's Hospital as outpatients between November 2015 and March 2016. This study was approved by the Institutional Review Board of St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Suwon, Korea. The methods were performed in accordance with the approved guidelines.

2.1 | Inclusion criteria

Female adults who were at least 20 years old and seeking to achieve a brighter facial skin tone were enrolled. The primary aim of this study was to enhance the background skin tone, rather than to treat a specific hyperpigmentation disorder. Therefore, patients with no

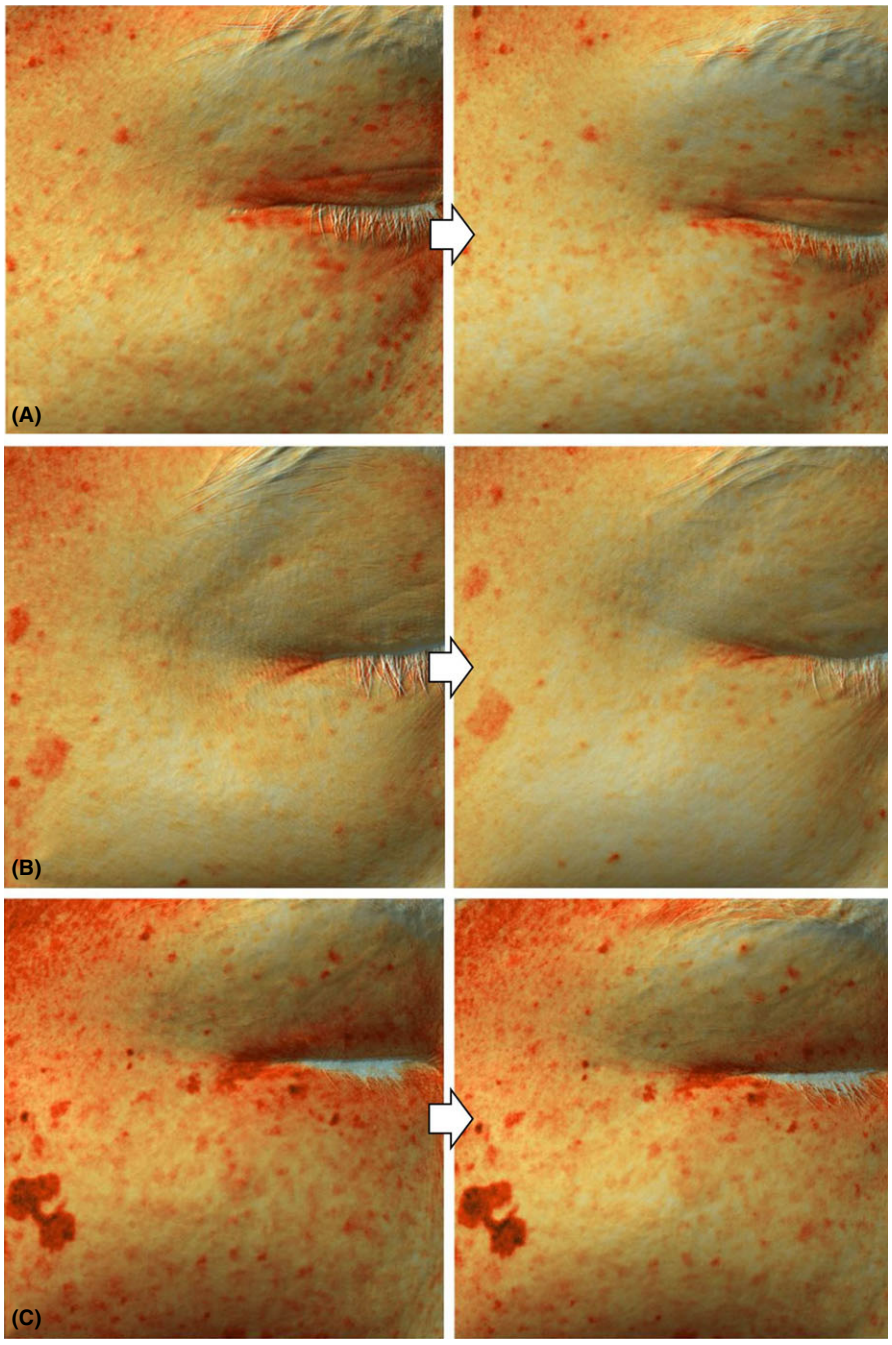

FIGURE 1 Clinical photographs with Antera 3D® indicate improvement after treatment with the new brightening cream. Compared to baseline, 12 weeks of treatment reduced facial hyperpigmentation significantly. (A), (B), and (C) refer to patient numbers 3, 15, and 2, respectively, before and after the 12-week treatment. A denser red color implies more intense melanin pigment

definite hyperpigmentation disorders as well as those with various facial hyperpigmentation except melasma were enrolled.

2.2 | Exclusion criteria

The exclusion criteria were as follows: pregnant or lactating women; those with melasma, active cutaneous infection, or any concurrent endocrine disorder; patients taking hormone replacement therapy or oral contraceptives; patients with a history of any other depigmenting treatment in the past 6 months; and patients with a history of laser or intense pulsed light therapy in the previous 6 months.

2.3 | Treatment

The brightening complex cream containing niacinamide 5.0%, tranexamic acid 2.0%, oxyresveratrol 2.0%, glutathione disulfide 2.0%, and linoleic acid 1% was applied to the face two times per day for 12 weeks.

2.4 | Outcome assessment

The observation period was 12 weeks in total. There was a baseline visit and then repeat visits at 4, 8, and 12 weeks. Standardized photographs by Janus Technology and Antera 3D® (Miravex, England) were taken at baseline and every 4 weeks thereafter until the 12th week.

2.5 | Objective measurement

Melanin index (MI), erythema index (EI), and chromatic aberration values (L*, a*, and b*) were measured. The MI and EI were measured using Mexameter® (MX 18, CK Electronic, Köln, Germany). Mexameter readings were performed in both lateral periocular areas. The chromatic aberration values (L*, a*, b* value) were also measured at both lateral periocular areas using the Spectrophotometer CM-2500d® (Konica Minolta, Japan).

2.6 | Clinical assessments

Improvement, as perceived by the investigators and patients, was measured using the investigator's global assessment (IGA) score and the patient's global assessment (PGA) score, respectively. Both assessments included a 5-point scale: −1=worse; 0=no improvement; 1=mild improvement; 2=moderate improvement; and 3=marked improvement. Scores were rated at 12 weeks by both the investigator and the patient.

2.7 | Statistical analysis

Repeated measures analysis of variance was conducted to evaluate the parameters according to the time point (V0, V4, V8, and V12). *Post hoc* analyses were conducted to determine the changes from baseline. The data were analyzed using R 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

All 26 female patients (23-49 years) completed the study. The mean age was 38 years. The patients held diagnoses of freckles, lentigines, or postinflammatory hyperpigmentation. The hyperpigmentation was significantly reduced after 12 weeks of treatment, as measured using image analysis by Antera 3D® (Figure 1).

3.1 | Objective measurements

The average MI decreased significantly at 12 weeks (35.2±4.8) compared to that at baseline (39.0±4.5) (Figure 2A). The average EI also decreased significantly from baseline (11.3±3.5) to 12 weeks

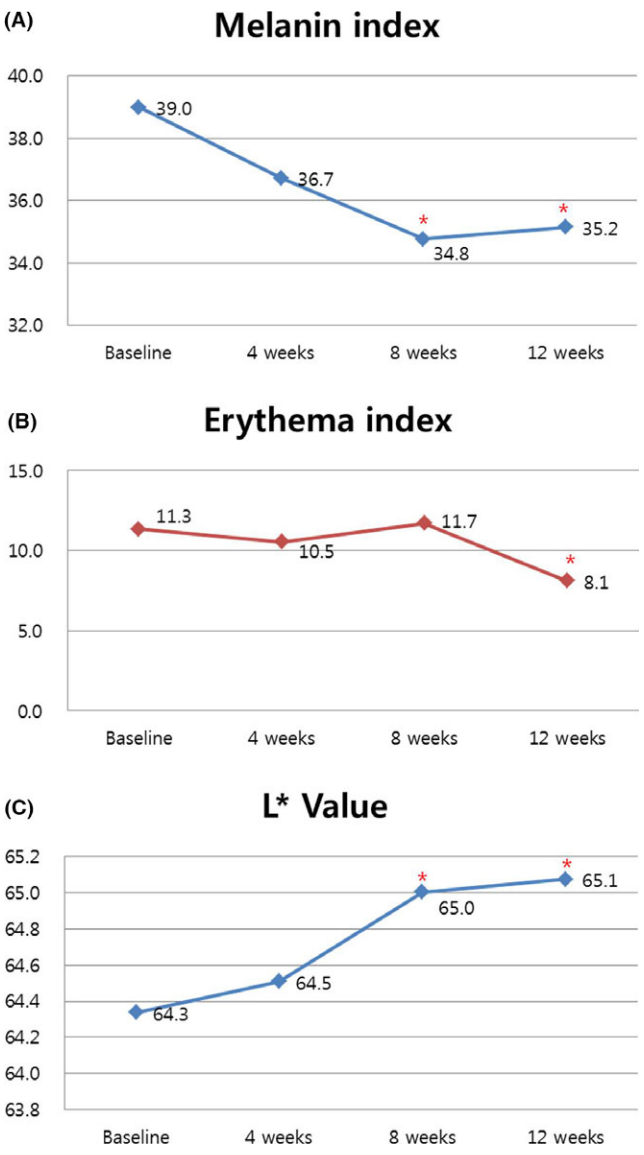

FIGURE 2 Changes in melanin index (MI), erythema index (EI), and chromatic aberration values after initiating treatment. (A) The MI was significantly decreased at 8 weeks ($P<.05$) and at 12 weeks ($P<.001$). (B) The EI was significantly decreased at 12 weeks ($P<.001$). (C) The L*-value, which reflects skin lightness, was increased significantly at 8 weeks ($P<.05$) and at 12 weeks ($P<.05$). (*P-value<.05)

TABLE 1 Improvements in melanin index (MI), erythema index (EI), and chromatic aberration values at each four-week follow-up visit. The 12-week treatment with the new brightening cream resulted in significant improvements in MI, EI, and skin lightness (L*-value) compared to those at baseline

	Baseline	4 weeks	8 weeks	12 weeks
Melanin index (mean±SD)	39.0±4.5	36.7±5.7	34.8±9.0*	35.2±4.8*
Erythema index (mean±SD)	11.3±3.5	10.5±2.4	11.7±8.5	8.1±2.2*
L* value (mean±SD)	64.3±2.1	64.5±2.5	65.0±2.5*	65.1±2.5*
a* value (mean±SD)	10.2±1.2	9.8±1.4	9.6±1.1*	9.6±1.2*
b* value (mean±SD)	19.3±1.7	19.8±1.8	19.5±1.8	19.2±1.9

SD, standard deviation; *P-value<.05.

(8.1±2.2) (Figure 2B). In addition, the average L* value, which reflects the skin lightness, increased significantly from baseline (64.3±2.1) to 12 weeks (65.1±2.5) (Figure 2C). The average MI and EI reductions (from baseline) were −3.8±4.8 (−9.7%) and −3.2±2.2 (−28.3%), respectively (both, P<.001) (Table 1).

3.2 | Clinical assessment

On the clinical evaluation at 12 weeks, there was good improvement in hyperpigmentation with regard to the color and size of the affected areas. Eighty-six percent of patients were rated 1 (=mild improvement) by IGA score, while 77% and 9% of patients were rated 1 (=mild improvement) and 2 (=moderate improvement), respectively, by the PGA score (Figure 3). There were no reported side effects in the 12-week study, including erythema, itching, scarring, skin atrophy, telangiectasia, or postinflammatory hyperpigmentation.

4 | DISCUSSION

Skin hyperpigmentation either results from overproduction of melanin by a physiological number of melanocytes or from an excessive number of melanocytes.[3] Melanin is synthesized in the melanosomes of melanocytes, which lie at the basal layer of the epidermis. Melanin-containing melanosomes are then transferred from the melanocytes to the keratinocytes, resulting in melanin distribution throughout the epidermis.[4] The key enzyme in melanin synthesis is tyrosinase (TYR). Ultraviolet exposure, chronic inflammation, aging, and hormonal changes may accelerate skin pigmentation.[5] Ultraviolet radiation triggers the formation of reactive oxygen species (ROS), which ultimately leads to melanogenesis.[6]

Skin brightening can be achieved through inhibition of one or more of the specific melanocyte maturation or distribution processes or by avoiding provoking factors such as ultraviolet radiation. Until recently, medical products including hydroquinone, tretinoin, and corticosteroid have been widely used to treat skin hyperpigmentation with favorable outcomes. However, these medical products are not easily accessible because medical supervision is mandatory for their use. In addition, various regulatory authorities have raised doubts over the safety of these compounds.[2,7] Tretinoin may cause skin irritation and aggravate skin inflammation, therefore limiting its tolerance and patient compliance. Hydroquinone use is prohibited in certain countries in Asia and Europe due to its adverse side effects, such as skin irritation, contact dermatitis, and exogenous ochronosis. These concerns have led to the development of alternative agents with better tolerance. These newer agents are also available for general, daily use as cosmetics. Nonetheless, the effectiveness of these alternative agents compared to tretinoin or hydroquinone has yet to be verified. A number of active ingredients are currently under study. Assuming that the combination of these ingredients may yield higher efficacy through a synergistic effect, efforts are being made to yield an effective combination of numerous ingredients. In this study, a number of brightening agents were studied, including niacinamide, tranexamic acid, oxyresveratrol, glutathione disulfide, and linoleic acid.

Niacinamide is the physiologically active amide of niacin (vitamin B3).[8] It is known that niacinamide has various effects on the skin. It acts as an anti-inflammatory agent and antioxidant and prevents photoimmunosuppression and photocarcinogenesis. Moreover, niacinamide have been reported to affect depigmentation of skin by preventing the transfer of melanosomes to keratinocytes.[9] In previous studies, the topical application of niacinamide resulted in a dose-dependent and reversible reduction in skin hyperpigmentation. Several clinical studies have shown that niacinamide has a higher tolerability and fewer side effects than hydroquinone.[10]

Topical tranexamic acid inhibits UV-induced plasmin activity in keratinocytes by preventing the binding of plasminogen and keratinocytes. This mechanism results in the suppression of UV-induced melanogenesis and reduced prostaglandin production. The depleted

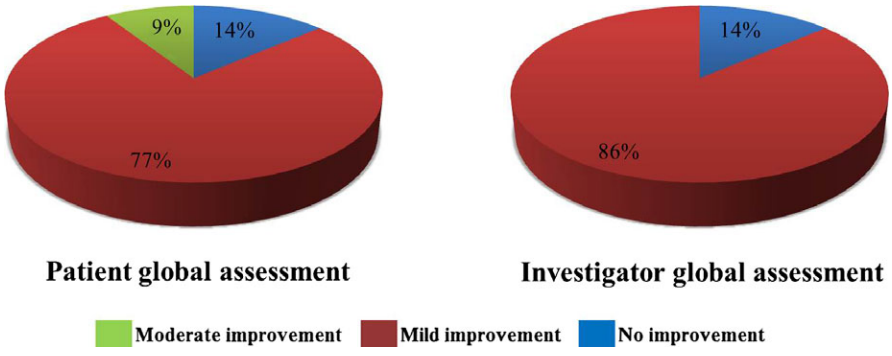

FIGURE 3 Patient and investigator global assessment scores after 12 weeks of treatment with the new brightening cream

production of prostaglandin reduces the melanocyte tyrosinase activity, ultimately brightening the skin.[11]

Oxyresveratrol is a phenolic compound derived from plants such as *Morus alba* Linne. One previous study suggested that the depigmenting effect of oxyresveratrol acts through the noncompetitive inhibition of tyrosinase activity, rather than suppression of the expression of tyrosinase.[12] In addition, oxyresveratrol showed a dose-dependent inhibitory effect on L-tyrosine oxidation by tyrosinases from mushroom and murine melanoma B-16.[12]

Glutathione disulfide is the oxidized form of glutathione, which is one of the nonenzymatic antioxidants that protects the skin. The nonenzymatic antioxidant systems in the skin include ascorbic acid in the fluid phase, glutathione in the cellular compartment, vitamin E in the membranes, and ubiquinol in the mitochondria. When the generated ROS is reduced by a-tocopherol, one form of vitamin E, the oxidized tocopherol can be regenerated by ubiquinol or ascorbic acid. In turn, glutathione can restore ascorbic acid from the oxidized to the reduced state. In doing so, glutathione activates these antioxidants to neutralize additional ROS.[13,14] Given that ROS induction leads to the activation of melanogenesis, glutathione, which facilitates ROS scavenging, is assumed to be beneficial for skin brightening.

Linoleic acid, an unsaturated fatty acid, is recently known to decrease melanin synthesis and tyrosinase activity.[15] Linoleic acid inhibits melanogenesis by accelerating the proteolytic degradation of tyrosinase in B16 murine melanoma cells.[16] It also accelerates the turnover of the stratum corneum, which results in the faster desquamation of melanin pigment from the epidermis.[17,18] One animal study found that the topical application of linoleic acid to the UV-stimulated hyperpigmented skin of brownish guinea pigs showed a pigment-lightening effect.[17]

In this study, we verified the efficacy of a new combination of brightening agents using objective parameters such as MI, EI, and L* value. After 12 weeks of treatment with a new complex cream, MI, EI, and L* value improved by 9.7%, 28.3%, and 1.2%, respectively. According to the IGA and PGA score, 86% of patients experienced mild or moderate improvement. This combination of new brightening agents did not have any of the side effects that are typically associated with the use of medical products such as hydroquinone and tretinoin. All of the involved patients tolerated the product without complication, which is of great importance for therapeutic compliance.

The main limitation of this study is the absence of a control group. Comparing the efficacy with medical products such as tretinoin or hydroquinone may have afforded a more accurate assessment of the product.

In conclusion, our data demonstrate that the brightening cream, composed of niacinamide, tranexamic acid, oxyresveratrol, glutathione disulfide, and linoleic acid, is safe and effective in Asian women.

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