

Effect of a Tranexamic Acid, Kojic Acid, and Niacinamide Containing Serum on Facial Dyschromia: A Clinical Evaluation

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ABSTRACT

Background: Stubborn dyschromia such as melasma and post-inflammatory hyperpigmentation (PIH) are leading causes for cosmetic consultation. Topical treatment is challenging, using a range of modalities, to stop, hinder, and/or prevent steps in the pigment production process. Tranexamic acid (TXA), a potent plasmin inhibitor, is proposed to control pigmentation by inhibiting the release of inflammatory mediators involved in triggering melanogenesis. TXA has been recently introduced as a topical therapy aimed at reducing pigmentation in melasma.

Methods: In a 12-week clinical study, a novel, topical facial serum containing 3% TXA, 1% kojic acid, and 5% niacinamide was evaluated for its effectiveness in treating melasma, PIH, and hyperpigmentation in Brazilian female subjects with Fitzpatrick skin types I-IV. Efficacy evaluations were performed at pre-treatment baseline, weeks 2, 4, 8, and 12, and included expert clinical grading, bio-instrumental measurements, and self-assessment questionnaires. Cutaneous tolerability was also evaluated by assessing subjective and objective irritation of the treatment area.

Results: A significant improvement in the appearance of PIH, hyperpigmentation, melasma, skin texture, and skin tone homogeneity was observed beginning at week 2 and continued through week 12. Melanin index, as measured by Mexameter®, demonstrated a significant decrease by week 12 as compared to both pre-treatment baseline and control.

Conclusions: The findings suggest that the test product is an effective and well-tolerated treatment option for addressing hyperpigmentary conditions, including melasma. Additional in vitro data suggests that TXA may act by mediating the inhibition of PGE2-stimulated human epidermal melanocytes.

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INTRODUCTION

The etiology of skin dyschromia remains complex and its treatment remains challenging, particularly for melasma. Melasma is a common, persistent disorder of hyperpigmentation affecting a significant portion of the population, particularly women living in areas with intense ultraviolet radiation.[1,2] It is characterized by symmetric hyperpigmented macules or patches with irregular borders, most often distributed on the forehead, cheeks, and along the jawline.[3,4] The causes of melasma remain unknown, although some triggering factors are described, such as sun exposure, pregnancy, use of oral contraceptives and steroids, hepatopathies, use of photosensitizing drugs, inflammatory processes of the skin, and stressful events.[5] Melasma, hyperpigmentation, and post-inflammatory hyperpigmentation (PIH), are prevalent in all Fitzpatrick skin types, especially in those with darker skin tones.[6] These dermatologic conditions are a leading cause for cosmetic consultation, and account for the high demand for effective skin lightening therapies.[7] Studies have shown that hyperpigmentation, particularly melasma, greatly affects quality of life, causing psychosocial distress.[8] Treatments for melasma include topical depigmenting agents, such as hydroquinone (HQ (2-4%)), tretinoin, azelaic acid, superficial peeling agents, and lasers. Results with these treatments are often temporary, as the discoloration generally returns with continued exposure to the sun.[9]

Kojic acid and niacinamide, two well-known skin lightening agents, either alone or in combination with other actives, have been demonstrated to be effective in reducing the hyperpigmentation, including melasma.[10-14] Tranexamic acid (trans-4-aminomethylcyclohexanecarboxylic acid: TXA) is a

plasmin inhibitor used to prevent fibrinolysis to reduce blood loss. It exerts its effect by reversibly blocking lysine binding sites on plasminogen, thus inhibiting plasminogen activator (PA) from converting plasminogen to plasmin. While plasminogen also exists in human epidermal basal cells and cultured human keratinocytes are known to produce PA, there is basic rationale that TXA may affect keratinocyte functions and interactions.[8] The anti-plasmin activity of TXA is thought as being the main mechanism of its hyperpigmentary effect. In several studies, treatment with topical TXA (2-5%) was shown to be well tolerated, with no serious side effects reported.[5,10]

In a 12-week, single-center, clinical study, a novel topical facial serum containing 3% tranexamic acid, 1% kojic acid, and 5% niacinamide, was evaluated for its effectiveness in treating mild to moderate melasma, PIH, and hyperpigmentation in Brazilian female subjects. Efficacy parameters included expert clinical grading, bioinstrumental measurement, self-assessment questionnaires, and subjective and objective cutaneous tolerability assessment. TXA's mechanism of action was also assessed utilizing in vitro cultures of human epidermal melanocytes.

METHODS

In vivo Clinical Study

The clinical study was conducted at a contract research organization (CRO) in São Paulo, Brazil from May to September 2017 (Allergisa-SP, Brazil). Written informed consent was obtained from all study subjects prior to enrollment. The study was conducted in accordance to the guidelines outlined by the Ethical Principles for Medical Research Involving Human Subjects- Helsinki Declaration (1964) and its successive updates.[16] The CRO adhered to the Good Clinical Practice (GCP) guidelines throughout the course of the study. An Independent Ethics Committee (IEC) (Investiga – Instituto de Pesquisas, registered by the National Research Ethics Commission (CONEP)) approved the study.

Formulation

The formulation evaluated was a hydroglycolic topical facial serum (Discoloration Defense, SkinCeuticals Inc., New York, NY) containing the following ingredients: 3% tranexamic acid (TXA), 1% kojic acid, 5% niacinamide, and 5% hydroxyethylpiperazine ethane sulfonic acid (HEPES).

Subjects

Fifty-five healthy Brazilian female subjects aged 27 to 60 years (mean age, 41 years) were enrolled in the 12-week clinical study. Subjects were non-smokers with Fitzpatrick skin types I-IV. At least 50% of subjects had self-perceived sensitive skin. The inclusion criteria for the study included a clinical evaluation score by a dermatologist on a visual analog scale for mild to moderate hyperpigmentation, skin texture roughness, and skin tone unevenness. A dermatologist identified mild to moderate PIH (according to a visual analog scale) in 36 of the 55 subjects, and mild to moderate melasma (according to a modified MASI scale) in 48 of the 55 subjects.

Treatment Protocol

The topical serum was evenly applied across a cleansed face in the morning and evening. The serum's first application was conducted at the CRO during the inclusion visit (Day 0). Following the inclusion visit, subjects applied the topical serum at home for 12 weeks (D1-D83). The subjects were also provided with a sunscreen (SPF 70), which was applied to the face in the morning and as needed throughout the day prior to sun exposure.

Evaluation Parameters and Methods

Assessment of Facial Dyschromia

Clinical scoring of melasma according to a modified MASI scale was conducted by a dermatologist at pre-treatment baseline and weeks 2, 4, 8, and 12 on 48 of the 55 subjects who were identified as having melasma. The modified MASI score was calculated by subjective assessment of two factors: area of involvement (A) and darkness (D), with the forehead (f), right malar region (rm), left malar region (lm), and chin (c), corresponding to 30%, 30%, 30%, and 10% of the total face, respectively.

The modified MASI was scored as follows and the range of the total score was 0 to 24:

$$mMASI=0.3A(f)D(f)+0.3A(lm)D(lm)+0.3A(rm)D(rm)+0.1A(c)D(c)$$

Expert clinical grading evaluations were conducted at pre-treatment baseline, weeks 2, 4, 8, and 12. Facial dyschromia parameters were clinically graded on a modified Griffith's 5-point scale, with half-point increments, where 0=none (best possible condition) and 4=severe (worst possible condition). Efficacy measures included visual evaluation and grading by a dermatologist under standard daylight assessing the following attributes: appearance of PIH, hyperpigmentation, and skin texture. Skin tone homogeneity was clinically graded on a 4-point scale, with half-point increments, where 0 =none (best possible condition) and 3=severe (worst possible condition).

Tolerability Assessment

Tolerability assessments were conducted at pre-treatment baseline, weeks 2, 4, 8, and 12. Tolerability parameters were graded on a scale where 0=none; 1=mild; 2=moderate; and 3=severe. Clinically-graded objective irritation parameters included erythema, dryness, scaling, and edema. In addition, subjects self-assessed burning, stinging, itching, tightness, and tingling.

Bioinstrumentation

Standardized digital photographs of subjects were taken at the

pre-treatment baseline, week 2, week 4, week 8, and week 12 time points using the VISIA-CR (Canfield Scientific, Fairfield, NJ) imaging system. Full frontal, left, and right profile views of the face were obtained, under standard visible, crossed-polarized, and parallel-polarized lights.

The melanin index (MI) and erythema index (EI) scores of lesional melasma and PIH skin were measured in triplicate using a colorimeter (Mexameter MX 18, Courage + Khazaka GmbH, Koln, Germany). Measurements of the lesional areas, as well as the adjacent perilesional normal skin (control site), were captured. The difference between the control and the lesional areas was calculated.

Subject Self-Assessment via Questionnaires

Subjects responded to questions regarding the formula's aesthetics and perceived efficacy throughout the course of the study.

Statistical Analysis

All subjects who completed the clinical study were included in the statistical analysis. Data were tested for normal distribution with the Shapiro-Wilk test, using a cutoff value of $P<0.01$ for efficacy and tolerability data. Efficacy and tolerability of the test serum was evaluated by comparing the post-treatment data to the pre-treatment baseline data for each attribute. The significance of change was determined using either a paired t-test for normally distributed data, or a Wilcoxon signed rank test for non-normal data. The cutoff value for significance was $P<0.05$. Instrumental data were similarly evaluated. The mean percent changes from pre-treatment baseline were reported at each time point for each attribute. The statistical analysis was carried out using the following software: MINITAB 14, STATA and XLSTAT 2017.

In Vitro Study

Monolayer Cultures of Human Epidermal Melanocytes

Inhibition by TXA on PGE2-induced melanogenesis was evaluated in cultured human epidermal melanocytes. Normal human epidermal melanocytes from four different donors obtained from ZenBio (Research Triangle Park, NC, USA) were plated at a density of 10,000 cells per cm^2 and grown in serum-free melanocyte growth medium. After 3 days, when the cells reached 70% confluence, medium was changed, and cells were treated over 72 hrs with 30 nM PGE2, and 50 or 100 µM TXA or combination of PGE2 (30 nM) + TXA (50 or 100 µM). Control cells were treated with equivalent amount of vehicle (ethanol for PGE2, water for TXA) without any active. After 4 days of cell growth, the cells were harvested, and the melanin content was analyzed using OD measurement at 405 nm. The cells were stained with Fontana Mason stain for melanin quantification.

RESULTS

In vivo Clinical Study Results

Assessment of Facial Dyschromia

All clinically-graded skin attribute parameters showed a statistically-significant decrease (improvement) in scores at all time points compared to baseline (Table 1). Improvements were apparent as early as 2 weeks and were maintained through the study conclusion (week 12). Significant improvements were observed in the appearance of PIH, hyperpigmentation, skin texture, and skin tone homogeneity. A significant reduction in melasma, as evaluated by the mMASI scale, was also observed as early as 2 weeks, and at all time points thereafter.

TABLE 1.

Clinical Scoring for Facial Dyschromia: Change from Baseline

Skin Parameters	Mean Change from Baseline (±SD)			
	Week 2	Week 4	Week 8	Week 12
Appearance of PIH (N= 36)	-0.31 (±0.28)	-0.77 (±0.42)	-1.07 (±0.42)	-1.24 (±0.40)
Appearance of Hyperpigmentation (N= 55)	-0.08 (±0.18)	-0.20 (±0.31)	-0.52 (±0.31)	-0.98 (±0.30)
Appearance of Melasma (mMASI) (N= 48)	-0.6 (±1.1)	-1.5 (±1.8)	-2.8 (±1.8)	-3.3 (±1.9)
Skin Texture (N= 55)	0.59 (±0.46)	0.97 (±0.48)	1.12 (±0.44)	1.24 (±0.42)
Homogeneity of skin tone (N= 55)	0.10 (±0.22)	0.38 (±0.32)	0.54 (±0.34)	0.72 (±0.38)

A negative value for PIH, hyperpigmentation, and mMASI indicates an improvement from baseline. A positive value for skin texture and skin homogeneity indicates improvement from baseline. All values are statistically significant with $P<0.001$.

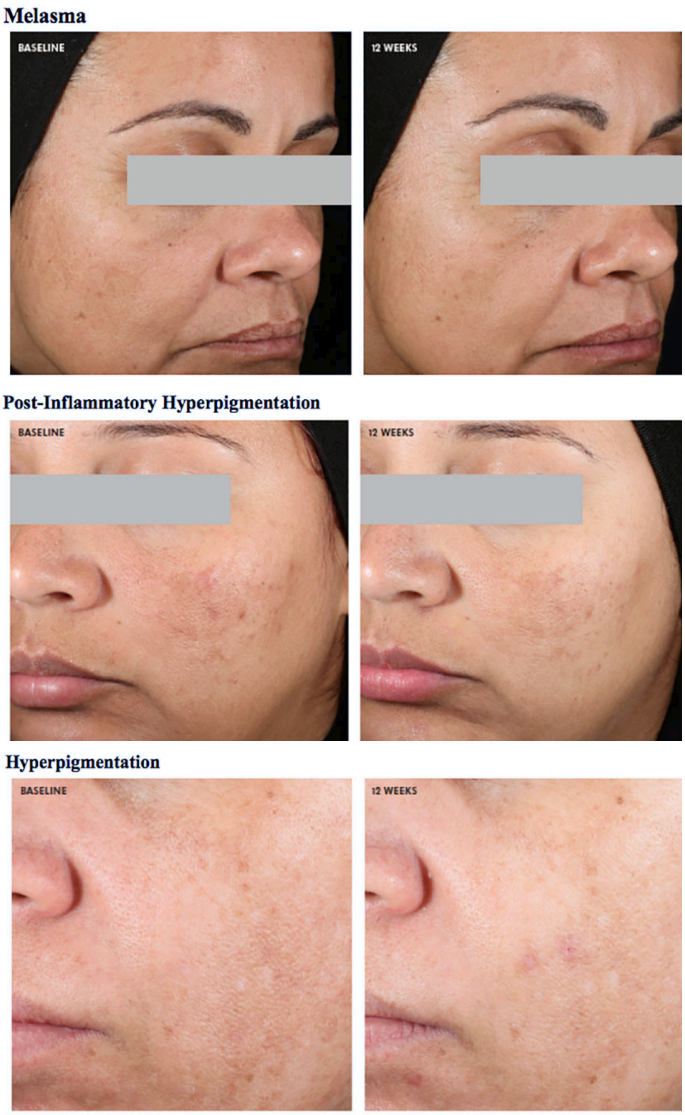
Standardized Photography – VISIA-CR

Standardized digital images of three selected study subjects at pre-treatment baseline (left) and week 12 (right) (Figure 1) demonstrated improvement in hyperpigmentation, PIH, and melasma, which were representative of average results for the overall study panel.

Mexameter® Measurements

Pigmentation measurements showed significant improvements compared to pre-treatment baseline (Table 2). The melanin index (MI) scores of the lesional melasma skin decreased significantly in as early as 4 weeks. By week 8, the lesional melasma skin showed a decrease in MI by as much as 9%. The perilesional normal skin (control site) also showed a significant decrease in MI by week 4. On week 8 and 12, the decrease in MI was significantly higher for the lesional melasma skin as compared to the control site ($P=0.008$ and $P=0.028$, respectively). This suggests that the topical serum had a greater effect in improving lesional melasma skin as compared to unaffected, normal skin.

FIGURE 1. Standardized digital images of selected study subjects at pre-treatment baseline (left) and week 12 (right), representative of average results for the overall study panel.



Similar results were observed for PIH. As early as 4 weeks, the melanin index of the lesional PIH skin significantly decreased, which continued through week 12. The perilesional normal skin (control site) also demonstrated a significant decrease in skin color with treatment at weeks 4 and 8. The decrease in MI was significantly greater in lesional PIH skin as compared to perilesional normal skin on week 2 (P=0.048), week 8 (P=0.002), and week 12 (P=0.014). The data demonstrates that the facial serum has greater efficacy on lesional PIH skin as compared to unaffected, normal skin.

The erythema index (EI) showed no significant change at most time points for both melasma and PIH. A significant decrease in EI scores was observed at week 8 for both the lesional melasma skin and perilesional normal skin, and week 8 for the lesional PIH skin, respectively (data not shown). However, no significant changes in EI were achieved in lesional skin as compared to perilesional normal skin for both melasma and PIH.

TABLE 2.

Instrumental Evaluation: Mexameter®				
Skin Parameters	Mean Change from Baseline (±SD) (value below is Mean % change from baseline)			
	Week 2	Week 4	Week 8	Week 12
Melasma area	-4.5 (±23.6) -1.5%	**-21.0** **(±27.5)** **-7.0%**	**-27.2** **(±25.2)** **-9.0%**	**-17.0** **(±28.0)** **-5.6%**
Control area	-2.9 (±21.0) -1.2%	**-14.8** **(±25.6)** **-6.5%**	**-17.9** **(±20.5)** **-7.8%**	**-8.3** **(±20.9)** **-3.7%**
Δ (Melasma – Control)	-1.7 (±18.8) -0.3%	-6.2 (±27.4) -0.5%	**-9.3** **(±23.2)** **-1.2%**	***-8.7*** ***(±26.5)*** ***-2.0%***
PIH	-11.6 (±37.4) -3.6%	**-18.6** **(±31.5)** **-5.8%**	**-30.6** **(±27.9)** **-9.5%**	**-22.9** **(±37.1)** **-7.1%**
Control	1.7 (±24.1) 0.7%	**-11.4** **(±29.0)** **-5.2%**	**-13.6** **(±23.8)** **-6.2%**	-6.3 (±20.5) -2.9%
Δ (PIH – Control)	***-13.3*** ***(±38.8)*** ***-4.4%***	-7.2 (±43.4) -0.6%	**-16.9** **(±29.7)** **-3.3%**	***-16.6*** ***(±38.4)*** ***-4.3%***

A negative mean change indicates improvement from baseline. Values in bold indicate statistical significance P<0.001. Values in bold and italics indicate statistical significance P≤0.05.

Self-Assessment Questionnaires

Overall satisfaction with the serum's aesthetics and efficacy were significant at all time points (data not shown).

Safety and Local intolerances

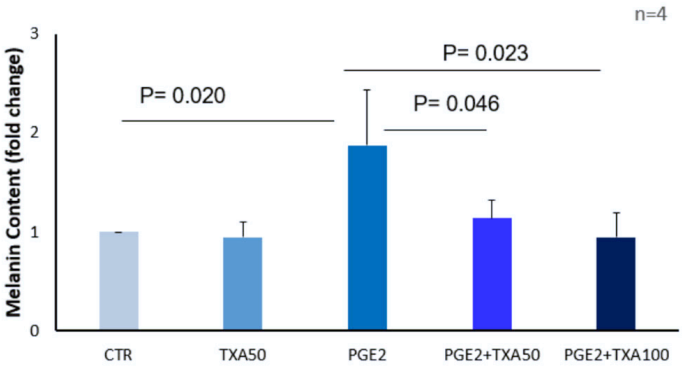
Local cutaneous tolerability was acceptable (data not shown). Minor transient effects such as erythema (2/55), itching (1/55), pruritis (1/55), redness (1/55), or stinging (1/55) were observed during the course of the study. Local intolerances were transient and quickly resolved after the product application. From the dermatologist's observation and conclusion, the product was considered to have very good tolerability and cutaneous acceptability.

In Vitro Study Results

TXA Inhibition of PGE2 Induced Melanogenesis

30nM PGE2 significantly stimulated melanin production in human epidermal melanocytes (HEM) compared to control cells (P=0.02; Figure 2). TXA alone showed no effect on melanin content of HEM. 50 µM and 100 µM TXA treatment of PGE2-stimulated melanocytes demonstrated a significant decrease in melanin content (P=0.046 and P=0.023, respectively. There was no significant difference between 50 µM TXA and 100 µM TXA.

FIGURE 2. TXA inhibition of PGE2-induced melanogenesis. A 10-day, in vitro study. PGE2-induced melanin production in human epidermal melanocytes (HEM) from four donors treated with TXA. 50 and 100 µM TXA inhibits PGE2-induced melanin production in Human Epidermal Melanocytes (HEM).



This in vitro study demonstrated that PGE2 stimulation is a reliable method for melanogenesis studies in normal human epidermal melanocytes. In this model, TXA dose dependently inhibited melanogenesis. The observation that TXA alone had no significant effect on melanogenesis also indicates that the mechanism of action of TXA involves blocking PGE2-induced melanin production in melanocytes.

DISCUSSION

It has been well established that TXA delivered orally or by injection is an effective approach in the treatment of melasma. However, only a limited number of studies have assessed the effectiveness of topical TXA on facial dyschromia. The objective of this study was to demonstrate the clinical efficacy of a novel topical facial serum containing 1% kojic acid, 5% niacinamide, and 3% TXA in improving key markers of discoloration. Kojic acid is a well-known skin-lightening agent that acts through inhibiting the rate limiting enzyme tyrosinase.[10,11] It has been suggested that niacinamide suppresses melanin transfer from melanocytes to keratinocytes.[13] Finally, we have established that TXA controls pigmentation by inhibiting the release of inflammatory mediators, specifically prostaglandins, which are involved in melanogenesis. Therefore, the combination of these three ingredients with distinct modes of action in an optimized hydroglycolic serum, synergistically target multiple biological pathways associated with the development of discoloration.

After 12 weeks of topical product application, an average 81% reduction in PIH was reported while melasma and hyperpigmentation improved by 60%. Marked improvements in skin tone and skin homogeneity were also observed, by 54% and 59%, respectively. The significant decrease in melanin index scores on melasma and PIH lesional skin compared to perilesional normal skin provides further evidence of product efficacy. In terms of perceived effectiveness, as measured by self-assessment questionnaires, subjects rated the topical serum highly favorable for both efficacy and aesthetics. Overall satisfaction with the serum was over 90% at all time points, which is promising considering the lack of satisfaction with non-prescription topical discoloration treatments.

The role of PGE2 in the signaling pathways involved in growth, differentiation, and apoptosis of melanocytes has been well-established.[23] PGE2 is also released abundantly by keratinocytes following exposure to UV radiation (UVR).[23,24] Keratinocyte-derived PGE2 stimulates the formation of dendrites in melanocytes and activates melanocyte and tyrosinase activity. TXA inhibits PG production, and thus reduces the melanocyte tyrosinase activity.[14] We demonstrated that 50-100 µM TXA suppressed the melanogenesis of PGE2-stimulated melanocytes in culture. This function of TXA is particularly relevant in the treatment of melasma, hyperpigmentation, and PIH.

In conclusion, this study demonstrates that a novel topical facial serum containing 3% TXA, 1% kojic acid, and 5% niacinamide, is a safe and effective treatment for melasma, hyperpigmentation, and PIH. In addition, TXA's mechanism of action has been further clarified by an in vitro study showing the suppression of PGE2-induced inflammation in normal human epidermal melanocytes.

DISCLOSURES

Dr. Desai, Dr. Ayres, and Dr. Bak have served as consultants to SkinCeuticals. Stephen Lynch, Susana Raab, Ana Du, DesTenee Green, Janet Wangari-Talbot, and Qian Zheng are employed by L'Oreal Research and Innovation. Cezary Skobowiat was employed by L'Oreal Research and Innovation at the time of this work. Megan Manco was employed by SkinCeuticals at the time of this work.

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