Received: 28 April 2020 | Revised: 19 May 2020 | Accepted: 4 June 2020

DOI: 10.1111/jocd.13545

ORIGINAL CONTRIBUTION

JCD Journal of Cosmetic Dermatology WILEY

New topical tranexamic acid derivative for the improvement of hyperpigmentation and inflammation in the sun-damaged skin

Ivan D. da Silva Souza PhD | Lorraine Lampe Bachelor of Chemistry Student | Daniel Winn PhD

Actera Ingredients Inc., Newtown, PA, USA

Correspondence
Ivan D. da Silva Souza, Actera Ingredients Inc., 66 Walker Lane, Newtown, PA 18940, USA.
Email: ssdivan@gmail.com

Abstract

Background: Skin-lightening products are used worldwide to treat persistent pigmentation disorders that impact our quality of life and self-confidence. However, consumers of cosmetic and over-the-counter skin lighteners struggle to find products that perform to their expectations. New, safe, and effective bioactives are needed to fill this gap.

Objective: To investigate the safety and skin-lightening performance of a new topical tranexamic acid derivative, that is, cetyl tranexamate mesylate.

Methods: The test material was a facial serum containing 2.0% (w/w) of the new bioactive. Safety was evaluated by a modified Human Repeat Insult Patch Test with 54 subjects of either sex. Performance was objectively assessed based on the improvement of melanin and erythema indexes through time, and also subjectively by photographs and self-perception questionnaires. Thirty-five female subjects applied the serum twice a day for 8 weeks.

Results: No questionable adverse reactions were observed. Melanin and erythema indexes improved significantly and continuously from the baseline to the end of the study (−16.9% and −34.3%, respectively). Photographs further support instrumental data. On average, after 2 weeks, the subjects already noticed an improvement in skin tone (79.3%), a reduction in dark spots (78.6%), and an improvement in facial redness (77.1%).

Conclusion: A topical serum containing cetyl tranexamate mesylate was well-tolerated and successfully improved the overall facial skin tone, as well as the appearance of dark spots and redness.

KEYWORDS

aging skin, dark spots, facial redness, photodamage, tranexamic acid

1 | INTRODUCTION

The use of skin-lightening products is widespread among consumers with pigmentation disorders.[1,2] Melasma and postinflammatory hyperpigmentation (PIH) are the most common facial dyschromia leading to the pursuit of skin homogeneity.[1] However, in a recent study, almost 60% of melasma and PIH patients were not satisfied with the level of improvement provided by their over-the-counter skin lighteners in the United States.[1] Common skin-lightening bioactives include hydroquinone, kojic acid, azelaic acid, steroids, retinoids, alpha-hydroxy acids, vitamins, and others.[1,2] Unfortunately, these bioactives have been linked to several adverse reactions, including epidermal

thinning, dryness, desquamation, stinging, erythema, skin irritation, allergic contact dermatitis, and even neuropathy.[2] Furthermore, hydroquinone is banned in the EU, and its use is restricted in many countries due to controversies around carcinogenesis.[2]

Because consumers are not achieving the desired level of improvement,[1] it is not surprising that the adulteration of skin lighteners with mercury to boost efficacy still is a prevalent global health hazard.[3] In fact, mercury-containing skin lighteners are still available for purchase in the United States,[3-5] UK,[6] EU,[7] China,[3] and other countries.[3,7] The US Food and Drug Administration restricts the amount of mercury in skin care products[3] because its prolonged use leads to severe autoimmune and renal dysfunctions.[6] Therefore, there is a legitimate need for new, safe, and effective skin-lightening bioactives.

Increasing evidence shows that tranexamic acid (TXA), a plasmin inhibitor, is an effective treatment for sunlight-induced dyschromia.[8-11] External skin disruptors, such as ultraviolet light or injuries, cause the keratinocytes to produce signal mediators (eg, plasminogen) that will start several processes, for example, inflammation, desquamation, melanocyte differentiation, increased tyrosinase activity, and transfer of melanosomes to upper skin layers. Although its mechanism of action still is under investigation, some have postulated that TXA decelerates these processes by interfering with plasmin activity, indirectly inhibiting melanogenesis.[8-13] Nonetheless, the permeability of TXA through the skin is insufficient due to its hydrophilic nature and strong hydrogen bonding capacity.[9,14] Esters of TXA present a higher level of skin targeting and could potentially be more efficient.[11,14]

The purpose of this study was to investigate the safety and skin-lightening performance of a new topical TXA ester salt, that is, cetyl tranexamate mesylate.

2 | METHODS

2.1 | Dermatological safety study

This study was a single-blind, single-center, Human Repeat Insult Patch Test (HRIPT) investigating the irritation and sensitization potential of a topical serum containing 2.0% (w/w) cetyl tranexamate mesylate (TeraCeutic TXVector™, Actera Ingredients). The test formulation also contained water, caprylic/capric triglyceride (5%, w/w), glycerin (2%, w/w), propanediol (2%, w/w), cetearyl alcohol (2%, w/w), glyceryl stearate (1%, w/w), tamarind gum (1%, w/w), phenoxyethanol (1%, w/w), and ethylhexylglycerin (0.2%, w/w). Fifty-seven healthy adult volunteers of either sex were subjected to a total of ten cutaneous occlusive patch applications (nine inductions and one challenge) for 47-48 hours each, based on a modified Draize method.[15] After removing the patches, a trained clinical grader assessed the application spots for visible signs of irritation or sensitization on a scale of 0 (no visible reaction) to 5 (bullous reaction). Three subjects quit for personal reasons. This research was sponsored by Actera Ingredients Inc, USA, and conducted by a contract research organization (Princeton Consumer Research Corp., UK) between July and August 2019, under the 1964 Declaration of Helsinki and its subsequent amendments.[16] The protocol was approved by the East Anglia Ethics Committee. All subjects provided written informed consent before participation.

2.2 | Clinical efficacy study

This study was a longitudinal, single-center, open-label, monadic, home-use, 8-week clinical study investigating the efficacy of the same topical serum containing 2.0% (w/w) cetyl tranexamate mesylate (TeraCeutic TXVector™, Actera Ingredients) in subjects with self-assessed uneven facial skin tone, dark spots, and redness. This research was sponsored by Actera Ingredients Inc, USA, and conducted by a contract research organization (Princeton Consumer Research Corp.) between October and December 2019, under the 1964 Declaration of Helsinki and its subsequent amendments.[16] All subjects provided written informed consent before participation. Twelve subjects also provided a written consent authorizing photography release and publication.

Participants were included if they were of legal age; healthy; female; with self-assessed uneven skin tone, dark spots (hyperpigmentation), and redness (inflammation); as well as willing to comply with the norms and procedures described in the informed consent document. Participants were excluded if they were allergic to facial products; pregnant or breast-feeding; regularly practiced more than 1 hour of outdoor activities under sunlight; presented observable pre-existing facial skin disease or condition; a history of insulin-dependent diabetes; a history of use of oral retinoids, topical retinoids, or immunosuppressants in the last 6 months; a history of facial treatments within 6 months of study start; a history of use of skin-lightening/-brightening products 2 weeks before study start; and/or were currently participating in other clinical trials involving the face.

Thirty-five healthy adult female volunteers were screened and recruited for the study. They were instructed to apply one full pump (about 1 mL) of the serum containing cetyl tranexamate mesylate to their face, twice a day, for 8 weeks. Volunteers were also (a) required to apply a broad-spectrum sunscreen of sun protection factor 50 or higher during daylight, (b) encouraged to avoid other facial care during the study, and (c) prohibited to use other products with lightening or brightening claims or ingredients. To ensure compliance during home use, all volunteers received training about the relevance of following the research guidelines, and they were tasked with keeping a study diary. At each visit, subjects were interviewed for compliance and had their diaries reviewed by the trained staff.

Variations in facial dark spots and redness were followed up and objectively evaluated by instrumental assessments at the baseline (week zero) and after 2 weeks, 4 weeks, and 8 weeks. Variations in facial skin tone, dark spots, and redness were also gauged subjectively by digital photographs and self-perception questionnaires

TABLE 1 Irritation and sensitization responses to the serum containing cetyl tranexamate mesylate[a]

Assessment timeline	Mean score[b,c]	n
Induction phase *(applied 47-48 h before the assessment)*		
Day 3	0.00 ± 0.00	57
Day 5	0.00 ± 0.00	57
Day 8	0.00 ± 0.00	57
Day 10	0.00 ± 0.00	57
Day 12	0.00 ± 0.00	56
Day 15	0.02 ± 0.13	55
Day 17	0.04 ± 0.19	54
Day 19	0.04 ± 0.19	54
Day 22	0.04 ± 0.19	54
Challenge phase *(applied on day 36)*		
Day 38 *(after 1 h)*	0.00 ± 0.00	54
Day 40 *(after 48 h)*	0.00 ± 0.00	54

[a]Based on a modified Draize method of Human Repeat Insult Patch Test (HRIPT).[15]

[b]A score of zero means no visible reaction, while a maximum score of five means a bullous reaction.

[c]Mean ± standard deviation.

using a 5-point Likert scale. Photographs were not processed or enhanced.

Facial skin pigmentation as a result of either melanin (dark spots) or hemoglobin (erythema or redness) was measured by a Mexameter® MX18 light probe (Courage + Khazaka Electronic, Germany) equipped to determine absorption and reflection at three wavelengths: green (568 nm), red (660 nm), and infrared (880 nm).[17] The probe allowed for a measuring surface of approximately 19.6 mm^2 (5 mm diameter) and measurement uncertainty of ±5%. Melanin and hemoglobin contents were represented by an arbitrary unit (0-999) correlated to the quantity of light absorbed by the skin. Melanin index was measured by the combination of two specific wavelengths (660 and 880 nm), corresponding to different absorption peaks of melanin pigments. In contrast, the erythema index was measured by a different combination of wavelengths (568 and 660 nm), corresponding to the absorption peak of hemoglobin subtracting the influence of other pigments, such as bilirubin. The face of each volunteer was inspected, and one visible dark spot and one visible redness area were measured on week zero and reassessed during each visit to the laboratory (measurement time = 1 second). Results were compared to the baseline.

2.3 | Statistics

Arithmetic means were presented with respective standard deviation. Mean percent improvement (reduction) from baseline was presented for each subsequent time point, per instrumental assessment. Paired t test was used to compare within-treatment variations from baseline and determine any significant difference. All statistical tests of hypothesis employed a level of significance of

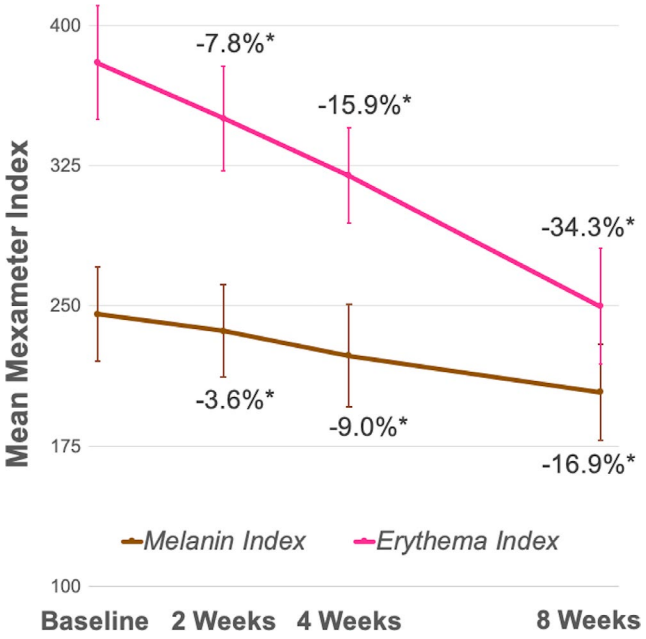

FIGURE 1 Variation and percent improvement of melanin and erythema mean indexes throughout the study. A negative mean percent change indicates an improvement from the baseline. *Significantly different from the baseline ($P < .01$). n = 35

FIGURE 2 Exemplary digital photographs of select study subjects at different time points

TABLE 2 Subjective assessment of the serum containing cetyl tranexamate mesylate

Self-perception statements:	Overall agreement (%)[a]	
After using the product…	After 2 wk	After 8 wk
1. I noticed an improvement in my skin tone.	79.3	83.6
2. I felt my complexion became more uniform.	77.1	82.9
3. I noticed a reduction in dark spots.	78.6	80.7
4. I felt my skin became clearer.	80.0	84.3
5. I noticed an improvement in blemishes on my skin.	78.6	83.6
6. The product improved the redness of my skin.	77.1	82.9
7. My skin looked less dull.	79.3	85.7
8. The brightness of my complexion improved.	80.0	82.9

[a]Calculated from the average score of a 5-point Likert scale, wherein 1 stands for strongly disagree and 5 for strongly agree. Results between 75% and 100% represent a stronger sense of agreement. n = 35.

5%. Average scores obtained from the questionnaires were used to calculate the overall agreement to specific subjective statements.

3 | RESULTS AND DISCUSSION

Fifty-four subjects completed the dermatological safety study (Table 1). No adverse events were reported during the study, and there was no record of adverse skin reactions such as dryness, scaling, stinging, papules, edema, or vesicles, of any intensity. From the sixth and seventh applications to the end of the induction phase, respectively, two subjects developed mild erythematous reactions (score 1—faint pink to definite pink). Overall, the serum containing cetyl tranexamate mesylate elicited faint, barely perceptible erythematous reactions during the induction phase of the study in a limited number of subjects (3.7%). There were no questionable reactions during the challenge phase by any of the subjects (no sensitization). The evidence supports that the test formulation is safe for skin.

At the beginning of the clinical efficacy study, all subjects presented signs of sun-damaged skin, such as uneven skin tone, hyperpigmentation (dark spots), and inflammation (facial redness). Some subjects also seemed to present dark spots characteristic of post-inflammatory hyperpigmentation (PIH), possibly related to acne lesions. All thirty-five subjects completed the clinical efficacy study. No adverse events or reactions were reported.

Follow-up of melanin and erythema indexes showed a significant reduction in pigmentation starting at the first time point, that is, after subjects applied the serum containing cetyl tranexamate mesylate for 2 weeks (Figure 1). Pigmentation continued to decrease linearly and significantly to the end of the study (Figure 1). Overall, the instrumental data suggest that the serum performed well for the aesthetic improvement of facial dyschromia related to melanin and hemoglobin, with remarkable performance in the case of facial redness.

Regarding the melanin index, most approaches for an effective improvement of hyperpigmented skin rely on a strategy with multiple bioactives. A gold standard prescription therapy based on the combination of hydroquinone (4%), tretinoin (0.05%), and fluocinolone acetonide (0.01%) was tested on female patients with mild-to-severe melasma, and it showed an improvement of −24.4% in melanin index after 8 weeks of treatment.[18] Even though no patient discontinued such therapy due to side effects, a considerable number of patients reported mild levels of erythema, scaling, and skin dryness.[18] On the other hand, a cosmetic serum containing tranexamic acid (3%), kojic acid (1%), niacinamide (5%), and hydroxyethylpiperazine ethane sulfonic acid (5%) was tested on female subjects with mild-to-moderate melasma or PIH, and it showed an improvement of −9.0% and −9.5% in melanin index after 8 weeks of study, respectively.[10] If compared to these cosmetic and prescription formulations,[10,18] topical cetyl tranexamate mesylate serum showed an intermediate performance (Figure 1), at a superior safety profile (Table 1). Neither of these studies noticed significant changes in erythema index.[10,18]

As for erythema index, our results were comparable to another study conducted under relatively similar conditions.[19] The authors tested a product containing 5% ascorbyl palmitate (vitamin C ester) on 30 women and reported −16% and −21% improvement in red areas after 4 and 6 weeks of application, respectively. However, 17% of the subjects in that study developed some type of adverse reaction to the vitamin C concentrate.[19]

These data also suggest that the new bioactive cetyl tranexamate mesylate has some advantages compared to tranexamic acid alone. As concluded from previous literature, topical tranexamic acid is efficient as a treatment for melasma, but its low hydrophobicity limits its permeation in the skin and impairs significant improvements in erythema.[9] Even though topical tranexamic acid improves hyperpigmentation, it does not seem to do so linearly and continuously through time,[9] as observed in this study with its ester salt derivative up to 8 weeks (Figure 1). In other words, topical cetyl tranexamate mesylate seems to promote a dual benefit, simultaneously improving facial dark spots and redness.

Digital photographs of three selected subjects of different age brackets demonstrated qualitative improvement in facial dark spots and redness compared to the baseline (Figure 2). These images were representative of average results for the overall study panel, and they further support the findings of the instrumental assessment.

Perception of improvement of facial dyschromia is a subjective matter contingent on the efficacy of the treatment, as well as on the discrepancy of individual expectations. In contrast to a previous report,[1] most subjects in this study noticed a satisfactory improvement in the uniformity of skin tone (Table 2, 1-2), reduction of dark spots (Table 2, 3-4), reduction of redness (Table 2, 5-6), and enhancement of skin radiance (Table 2, 7-8) soon after trying the serum containing cetyl tranexamate mesylate for 2 weeks. After 8 weeks of treatment, slightly more subjects perceived satisfactory improvement and agreed to all statements (Table 2). At the end of the study, all subjects agreed or strongly agreed that they were satisfied with this formulation.

A limitation of this study is that there was no placebo control group. Results need to be confirmed with large double-blind controlled trials. Also, comparisons with other bioactives did not take into account any potential effects of different formulations.

4 | CONCLUSION

A topical serum containing cetyl tranexamate mesylate was well-tolerated and successfully improved the overall facial skin tone, as well as the appearance of dark spots and redness. Whether objectively or subjectively, this study showed that cetyl tranexamate mesylate is a legitimate candidate for new, safe, and efficient skin-lightening bioactive.

ACKNOWLEDGMENTS

The authors thank all subjects for their participation in the study. We also thank the team at Princeton Consumer Research for their assistance with the study management, in particular Faye Scott, Jack Donnelly, and Lisa Long.

CONFLICT OF INTEREST

This study was fully sponsored by Actera Ingredients, a cosmetic and personal care supplier. All authors were affiliated with Actera Ingredients during the conduction of this study.

ORCID

Ivan D. da Silva Souza https://orcid.org/0000-0001-6176-1135

REFERENCES

1. Saade DS, Maymone MBC, Secemsky EA, Kennedy KF, Vashi NA. Patterns of over-the-counter lightening agent use among patients with hyperpigmentation disorders: a United States-based cohort study. *J Clin Aesthetic Dermatol*. 2018;11(7):26-30.
2. Burger P, Landreau A, Azoulay S, Michel T, Fernandez X. Skin whitening cosmetics: feedback and challenges in the development of natural skin lighteners. *Cosmetics*. 2016;3(4):36.
3. Hamann CR, Boonchai W, Wen L, et al. Spectrometric analysis of mercury content in 549 skin-lightening products: is mercury toxicity a hidden global health hazard? *JAAD*. 2014;70(2):281-287.
4. Engler DE. Mercury bleaching creams. *JAAD*. 2005;52(6):1113-1114.
5. Keefe S, Abdulle A, Holzer K, et al. Hmong College student perceptions and experiences with mercury containing skin lightening products in St. Paul Minnesota. *Hmong Stud J*. 2018;19(2):1-34.
6. Chakera A, Lasserson D, Beck-Jr LH, Roberts ISD, Winearls CG. Membranous nephropathy after use of UK-manufactured skin creams containing mercury. *Q J Med*. 2011;104:893-896.
7. Mohammed T, Mohammed E, Bascombe S. The evaluation of total mercury and arsenic in skin bleaching creams commonly used in Trinidad and Tobago and their potential risk to the people of the Caribbean. *J Public Health Res*. 2017;6:1097.
8. Lee DH, Oh IY, Koo KT, et al. Reduction in facial hyperpigmentation after treatment with a combination of topical niacinamide and tranexamic acid: a randomized, double-blind, vehicle-controlled trial. *Skin Res Technol*. 2014;20:208-212.
9. Kim SJ, Park JY, Shibata T, Fujiwara R, Kang HY. Efficacy and possible mechanisms of topical tranexamic acid in melasma. *Clin Exp Dermatol*. 2016;41:480-485.
10. Desai S, Ayres E, Bak H, et al. Effect of tranexamic acid, kojic acid, and niacinamide containing serum on facial dyschromia: a clinical evaluation. *J Drugs Dermatol*. 2019;18(5):454-459.
11. George A. Tranexamic acid: an emerging depigmenting agent. *Pigment Int*. 2016;3(2):66-71.
12. Denda M, Kitamura K, Elias PM, Feingold KR. Trans-4-(Aminomethyl) cyclohexane Carboxylic Acid (T-AMCHA), an anti-fibrinolytic agent, accelerates barrier recovery and prevents the epidermal hyperplasia induced by epidermal injury in hairless mice and humans. *J Invest Dermatol*. 1997;109(1):84-90.
13. Maeda K, Tomita Y. Mechanism of the inhibitory effect of tranexamic acid on melanogenesis in cultured human melanocytes in the presence of keratinocyte-conditioned medium. *J Health Sci*. 2007;53(4):389-396.
14. Hsieh P, Chen W, Aljuffali IA, Chen C, Fang J. Co-drug strategy for promoting skin targeting and minimizing the transdermal diffusion of hydroquinone and tranexamic acid. *Curr Med Chem*. 2013;20(32):4080-4092.
15. Jordan WP Jr, King SE. Delayed hypersensitivity in females. The development of allergic contact dermatitis in females during the comparison of two predictive patch tests. *Contact Dermatitis*. 1977;3(1):19-26.
16. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for Medical Research Involving Human Subjects. *JAMA*. 2013;310(20):2191-2194.
17. Tian Y, Wang YX, Gu WJ, Zhang P, Sun Y, Liu W. Physical measurement and evaluation of skin color changes under normal condition and post-ultraviolet radiation: a comparison study of Chromameter CM 2500d and Mexameter MX18. *Skin Res Technol*. 2011;17(3):304-308.
18. Nasrollahi SA, Nematzadeh MS, Samadi A, et al. Evaluation of the safety and efficacy of a triple combination cream (hydroquinone, tretinoin, and fluocinolone) for treatment of melasma in Middle Eastern skin. *Clin Cosmet Invest Dermatol*. 2019;12:437-444.
19. Jaros A, Zasada M, Budzisz E, Dębowska R, Gębczynska-Rzepka M, Rotsztejn H. Evaluation of selected skin parameters following application of 5% vitamin C concentrate. *J Cosmet Dermatol*. 2019;18:236-241.

How to cite this article: da Silva Souza ID, Lampe L, Winn D. New topical tranexamic acid derivative for the improvement of hyperpigmentation and inflammation in the sun-damaged skin. *J Cosmet Dermatol*. 2020;00:1–5. https://doi.org/10.1111/jocd.13545